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Dennis P. Tramaloni
(Print Name)

(Signature)

Date: June 07, 2001

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1626

Michael John Broadhurst, et al.

Serial No.: 09/779,116

Filed: February 8, 2001

For: **OXAMIDE IMPDH INHIBITORS**

TRANSMITTAL OF CERTIFIED COPIES

June 07, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Attached please find the certified copies of the foreign applications from which priority is claimed for this case:

Country	Application No.	Filing Date
Great Britain	0004392.7	February 24, 2000
Great Britain	0015877.4	June 28, 2000
Great Britain	0020322.4	August 17, 2000

Respectfully submitted,

Dennis P. Tramaloni
Attorney for Applicant
Reg. No. 28542
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110
Phone: (973) 235-4475

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Enclosures
54020

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Dated 13 December 2000

Patents Form 1/77

Patents Act 1977
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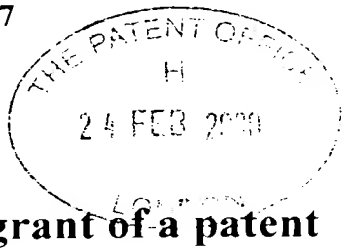

The Patent Office

1/77

Request for grant of a patent

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference: P14146GB-KR/GDP/mf

2. Patent application number *(The Patent Office will fill in this pa)*: **0004392.7**

24 FEB 2000

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*:

F.Hoffmann-La Roche AG,
124 Grenzacherstrasse,
CH-4070 Basle,
Switzerland.

Patents ADP number *(if you know it)*:

If the applicant is a corporate body, give the country/state of its incorporation: Switzerland

4. Title of the invention: Oxamide Derivatives

5. Name of your agent *(if you have one)*: Forrester Ketley & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*:

Forrester House
52 Bounds Green Road
London N11 2EY

Patents ADP number *(if you know it)*: 133001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

YES

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document.

Continuation sheets of this form	-
Description	80
Claim(s)	12
Abstract	1
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translation of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent based on the basis of this application

Forrester-Ketley & Co

Signature

Forrester Ketley & Co.

Date

24 February 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

Kate Richardson

0181 889 6622

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) if you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered "Yes" Patents Form 7/77 will need to be filed.

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Oxamide Derivatives

The present invention relates to novel oxamide derivatives, a process for their manufacture, pharmaceutical preparations containing these derivatives, and the use of these derivatives as medicaments. In particular, the present invention relates to novel oxamide derivatives which are inhibitors of inosine monophosphate dehydrogenase (IMPDH).

Inosine monophosphate dehydrogenase (IMPDH) is an enzyme involved in the de novo synthesis of guanine nucleotides. The enzyme catalyses the NAD-dependent oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate which is the rate limiting step in the synthesis of guanine nucleotides. As a result of the key role of the enzyme in guanine nucleotide biosynthesis, the enzyme represents an important target for the development of inhibitors which would have utility as therapeutic agents in the treatment of IMPDH related processes.

The de novo synthesis of guanine nucleotides is particularly important in B- and T-lymphocytes to provide sufficient levels of nucleotides to support a proliferative response to mitogen or antigen [Wu, J.C., Persp. in Drug Discovery and Design., 2, 185-204, (1994)]. IMPDH inhibition is thus an attractive target for selectively inhibiting the immune system. Inhibitors of IMPDH are known [Pankiewicz, K.W., Exp. Opin. Ther. Patents., 9, 55-65, (1999)], and the uncompetitive inhibitor mycophenolic acid (MPA) has been demonstrated to inhibit the response of B-and T-cells to mitogen or antigen [Allison, A.C. and Eugui, E.M., Transplant. Proc., 25, 8-18, (1993)]. MPA has therefore been utilised as an immunosuppressant.

It is also recognised that IMPDH plays a role in other rapidly proliferating cells such as tumour cell lines, indicating that IMPDH inhibition is a target for anti-cancer chemotherapy [Nagai, M. et al., 51, 3886-3890, (1990)].

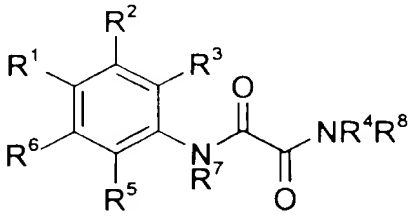
IMPDH inhibition has also been shown to play a role in viral replication in some cell lines which support virus replication [Pankiewicz, K.W., Exp. Opin. Ther. Patents., 9,

55-65, (1999)]. Ribavirin, for example, is a broad spectrum antiviral agent which has been approved by the U.S. Food and Drug Administration for use as an aerosol for infants with serious respiratory infections due to respiratory syncytial virus and is also in use as an agent for the treatment of patients infected with Hepatitis C virus when used in combination with interferon [Patterson, J.L. and Fernandez-Larsson, R., Rev. Infect. Dis., 12, 1139-1146, (1990); McHutchison, J.G. et al., New. Engl. J.Med., 339, 1549-1550, (1998)]. Ribavirin is converted in cells to ribavirin 5' monophosphate which is an inhibitor of IMPDH.

Additionally, the IMPDH inhibitors ribavirin and MPA have been shown to inhibit the replication of yellow fever virus (a RNA virus) whilst MPA has been demonstrated to inhibit Hepatitis B virus replication (a DNA virus) in vitro supporting the broad range antiviral activity of these inhibitors [Neyts, J. et al., Antiviral Res., 30, 125-132, (1996); Gong, Z.J. et al., J. Viral Hepatitis., 6, 229-236, (1999)]. Furthermore, MPA has also been shown to potentiate the antiviral effects of nucleoside analogues both in vitro and in animal models [Neyts, J. and De Clercq, E., Inter. Antiviral News., 7, 134-136, (1999)]. Together these observations indicate that IMPDH inhibitors have utility as broad spectrum antiviral agents.

IMPDH inhibitors would therefore have therapeutic potential as immunosuppressants, anti-cancer agents and anti-viral agents. Specifically, such compounds may be used in the treatment of transplant rejection, the treatment of cancer and as antiviral agents in the treatment of viral diseases such as retroviral infections and hepatitis C virus infections (either alone or in combination with other antiviral agents such as interferon or derivatives thereof, such as conjugates with polyethylene glycol).

The novel oxamide derivatives provided by the present invention are compounds of the general formula:



(I)

wherein

R^1 represents heterocyclyl;

R^2 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, hydroxy or cyano;

R^3 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^4 represents hydrogen, lower alkyl, lower cycloalkyl, aryl, or heterocyclyl;

R^5 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^6 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^7 represents hydrogen, or unsubstituted lower alkyl;

R^8 represents hydrogen, or unsubstituted lower alkyl;

or R^4 and R^8 together with the nitrogen atom to which they are attached represent heterocyclyl;

and pharmaceutically acceptable salts thereof.

The oxamide derivatives provided by the present invention are inhibitors of the enzyme inosine monophosphate dehydrogenase (IMPDH). They can be used as medicaments, especially for treating immune mediated conditions or diseases, viral diseases, bacterial diseases, parasitic diseases, inflammation, inflammatory diseases, hyperproliferative vascular diseases, tumours, and cancer. They can be used alone, or in combination with other therapeutically active agents, for example, an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-parasitic agent, an anti-inflammatory agent, an anti-fungal agent and/or an anti-vascular hyperproliferation agent.

In particular, compounds of the present invention and compositions containing the same are useful as chemotherapeutic agents, inhibitors of viral replication and modulators of the immune system, and can be used for the treatment of viral diseases such as retroviral infections and hepatitis C virus infections (either alone or in combination with other antiviral agents such as interferon or derivatives thereof, such as conjugates with polyethylene glycol), inflammatory diseases such as osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, and adult respiratory distress syndrome, hyperproliferative vascular diseases such as restenosis, stenosis and artherosclerosis, cancer, for example lymphoma and leukaemia, and as immunosupressants in the treatment of autoimmune diseases, graft versus host diseases and transplant rejection

Compounds of the present invention which have antiviral effects and/or immuno-supressive properties are particularly useful for treating HCV infection.

As used herein, the term "lower alkyl", means a straight-chain or branched-chain alkyl group containing up to 10 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to 6 carbon atoms, e.g.methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.butyl, tert-butyl, n-pentyl, n-hexyl and 1,1-dimethylethyl; and which is optionally substituted by e.g. one or more of cyano, halo, carboxyl, hydroxyl, lower alkoxy, heterocyclyl -(lower alkoxy)-aryl-amino-oxalyl-oxy, lower alkoxy-carbonyl, aryl, aryl-carbonyl-amino-aryl, lower alkyl-carbonyl-amino-aryl, heterocyclyl, lower alkyl-heterocyclyl, lower cycloalkyl, lower alkenyl, lower alkynyl, amino, mono- or di-(lower alkyl) amino, lower alkyl-aryl-lower alkyl-amino, lower alkoxy-carbonyl-amino, lower alkenyl-carbonyl-amino, lower alkyl-carbonyl-amino, di-(aryl)-lower alkyl-carbonyl-amino, lower alkyl-sulphonyl-lower alkyl-carbonyl-amino, lower cycloalkyl-lower alkyl-carbonyl-amino, heterocyclyl-lower alkyl-carbonyl-amino, lower alkoxy-lower alkyl-carbonyl-amino, di-aryl-lower alkyl-carbonyl-amino, aryl-carbonyl-amino, lower alkyl-aryl-carbonyl-amino, tri-(lower alkyl)-aryl-carbonyl-amino, mono- or di-(lower alkoxy)-aryl-carbonyl-amino, di-(lower alkyl)-amino-aryl-carbonyl-amino, lower alkyl-carbonyl-amino-aryl-carbonyl-amino, heterocyclyl-aryl-carbonyl-amino, lower cycloalkyl-carbonyl-amino, mono- or tetra-(lower alkyl)-lower cycloalkyl-carbonyl-

amino, heterocyclyl-carbonyl-amino, mono- or di-(lower alkyl)-heterocyclyl-carbonyl-amino, tri-(lower alkyl)-aryl-oxalyl-amino, lower alkyl-carbamoyl, or aryl-carbamoyl. Where there is more than one substituent, each substituent may be the same or different, for example tri-fluoromethyl, triphenylmethyl, 1-[1-methyl-1-[methylformyl]-2-phenyl] ethyl, or 2-[1-hydroxyl-3-cyclohexyl].

The term "unsubstituted lower alkyl" means an alkyl group as defined above where no substituents are present.

The term "lower alkenyl" means an alkenyl group containing from 2 to 7 carbon atoms, e.g. allyl, vinyl and butenyl.

The term "lower alkynyl" means an alkynyl group containing from 2 to 7 carbon atoms, e.g. propargyl or butynyl.

The term "lower cycloalkyl", alone or in combination as in "lower cycloalkyl-lower alkyl", means a cycloalkyl group containing 3 to 10 carbon atoms, preferably 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantyl, and which may be optionally substituted by e.g. one or more of lower alkyl, hydroxyl or aryl. Where there is more than one substituent, each substituent may be the same or different. Cyclopropylmethyl, 2-cyclobutyl-ethyl and 3-cyclohexyl-propyl are examples of lower cycloalkyl-lower alkyl groups.

The term "halo" denotes fluorine, chlorine, bromine or iodine.

The term "lower alkoxy" denotes a lower alkyl group as defined hereinbefore, which is bonded via an oxygen atom, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert.butoxy and the like.

The term "aryl", alone or in combination as in "aryl-lower alkyl", means phenyl or naphthyl, optionally benz-fused, for example benz-fused to a lower cycloalkyl ring, and/or optionally substituted by e.g. one or more of halo, cyano, lower alkyl-thio,

nitro, oxo, hydroxyl, lower alkoxy, lower alkyl-heterocyclyl, heterocyclyl, lower alkoxy-carbonyl, lower alkyl-carbonyl, heterocyclyl-carbonyl, lower alkyl-heterocyclyl-carbonyl, sulphamoyl, lower alkyl- sulphamoyl, lower alkyl-sulphonyl, heterocyclyl-sulphonyl, amino, mono- or di-(lower alkyl) amino, lower alkyl-sulphonyl-amino, di-(lower alkyl)-heterocyclyl-amino, lower alkyl-carbonyl-amino, (lower alkyl-carbonyl)(lower alkyl)-amino, lower alkoxy-carbonyl-amino, aryl-carbonyl-amino, mono- or di-(lower alkyl)-carbamoyl, aryl-carbamoyl, lower alkyl, aryl-lower alkyl, amino-lower alkyl, heterocyclyl-lower alkyl, lower alkoxy-carbonyl-lower alkyl, lower alkyl- sulphamoyl-lower alkyl, aryl-sulphonyl-amino-lower alkyl, lower alkyl-sulphonyl-amino-lower alkyl, lower alkoxy-carbonyl-amino-lower alkyl, heterocyclyl-oxy-carbonyl-amino-lower alkyl, aryloxy-carbonyl-amino-lower alkyl, lower alkyl-carbonyl-amino-lower alkyl, lower alkoxy-carbonyl-(lower alkyl)-amino-lower alkyl, lower alkyl-carbamoyl-lower alkyl, lower alkyl-aryl-carbonyl-amino-lower alkyl, aryl-carbamoyl-lower alkyl, lower cycloalkyl-carbonyl-amino-lower alkyl, heterocyclyl-carbonyl-amino-lower alkyl, or aryl-carbonyl-amino-lower alkyl. Where there is more than one substituent, each substituent may be the same or different, for example 1-(3-methoxy-4-oxazolyl)phenyl, 1-(3-chloro-4-methoxy)phenyl, 1-(3-chloro-4-methyl) phenyl, and 1-(3-fluoro-4-methyl)phenyl.

The term "aryloxy" denotes an aryl group as defined hereinbefore, which is bonded via an oxygen atom, e.g. phenoxy, and the like.

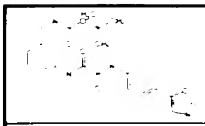
As used herein, the term "heterocyclyl", alone or in combination as in "heterocyclyl-lower alkyl", means a saturated, unsaturated or partially saturated monocyclic or bicyclic ring system which contains one or more hetero atoms selected from nitrogen, sulphur and oxygen; and which is attached to the rest of the molecule via a carbon atom (C-linked), or a nitrogen atom (N-linked) in the ring system, and which is optionally substituted in the same manner as the aryl group defined hereinbefore and/or by oxido. Where there is more than one substituent, each substituent may be the same or different. Examples of heterocyclyl groups are oxazolyl, isoxazolyl, furyl, tetrahydrofuryl, 1,3-dioxolanyl, dihydropyranyl, thienyl, pyrazinyl, isothiazolyl, isoquinolinyl, indolyl, indazolyl, quinolinyl, dihydrooxazolyl, pyrimidinyl, benzofuranyl, tetrazolyl,

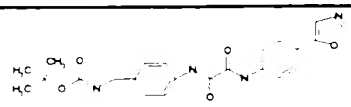
pyrrolidinonyl, (N-oxide)-pyridinyl, pyrrolyl, triazolyl e.g. 1,2,4-triazolyl, pyrazolyl, benzotriazolyl, piperidinyl, morpholinyl, thiazolyl, pyridinyl, dihydrothiazolyl, imidazolidinyl, pyrazolinyl, benzothienyl, piperazinyl, imidazolyl, thiadiazolyl e.g. 1,2,3-thiadiazolyl, and benzothiazolyl.

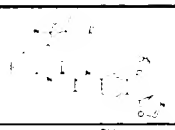
Any functional (i.e. reactive) group present in a side-chain may be protected, with the protecting group being a group which is known per se, for example, as described in "Protective Groups in Organic Synthesis", 2nd Ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1991. For example, an amino group can be protected by a tert.-butoxycarbonyl, formyl, trityl, benzyloxycarbonyl, 9-fluorenylmethyloxcarbonyl (Fmoc), trifluoroacetyl, 2-(biphenylyl)isopropoxycarbonyl or isobornyloxycarbonyl group or in the form of a phthalimido group; or a hydroxyl group can be protected by a tert.butyldimethylsilyl, tetrahydropyranyl, 4-methoxybenzyl, or benzyl; or a carboxyl group can be protected in the form of an ester, for example as a methyl or tert.butyl ester. The protecting group may be retained in the final compound or optionally removed by techniques known in the art.

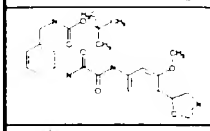
The compounds of this invention may contain one or more asymmetric carbon atoms and may therefore occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Furthermore, where a compound of the invention contains an olefinic double bond, this can have the (E) or (Z) configuration. Also, each chiral centre may be of the R or S configuration. All such isomeric forms of these compounds are embraced by the present invention.

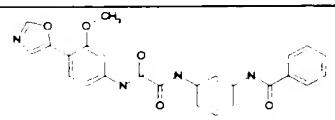
Examples of compounds of formula (I) are shown below in Table 1:

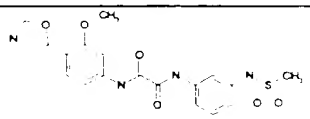


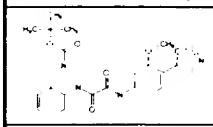


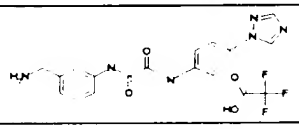


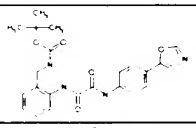


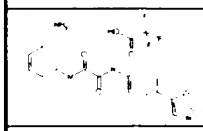


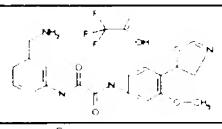


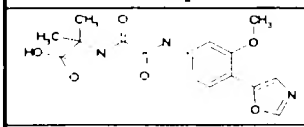


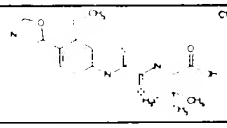


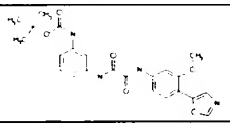


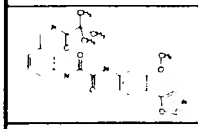


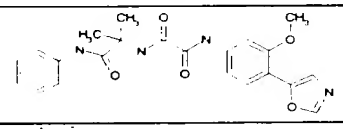


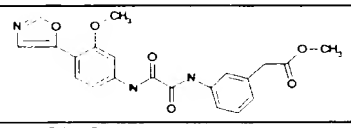


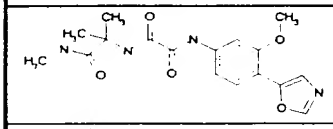


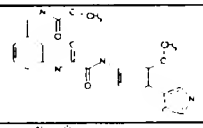


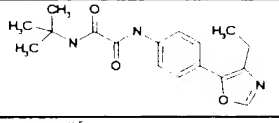


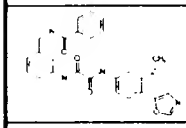


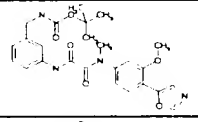


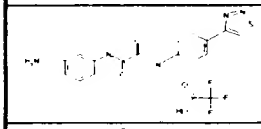


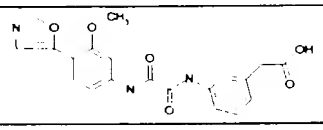


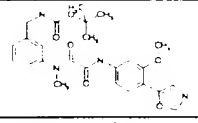


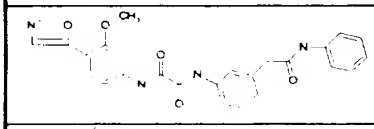


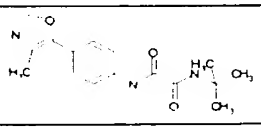


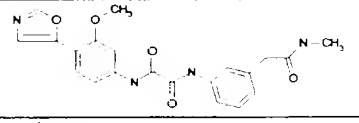


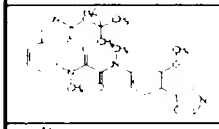


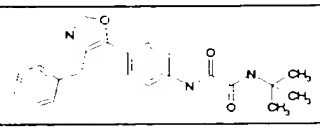


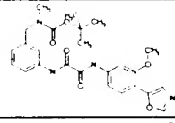


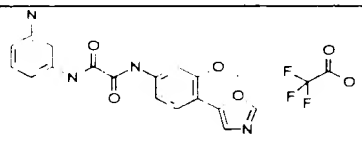


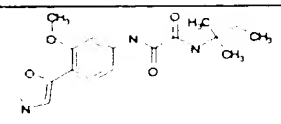


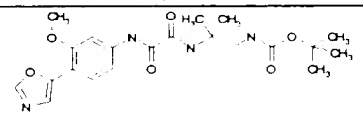












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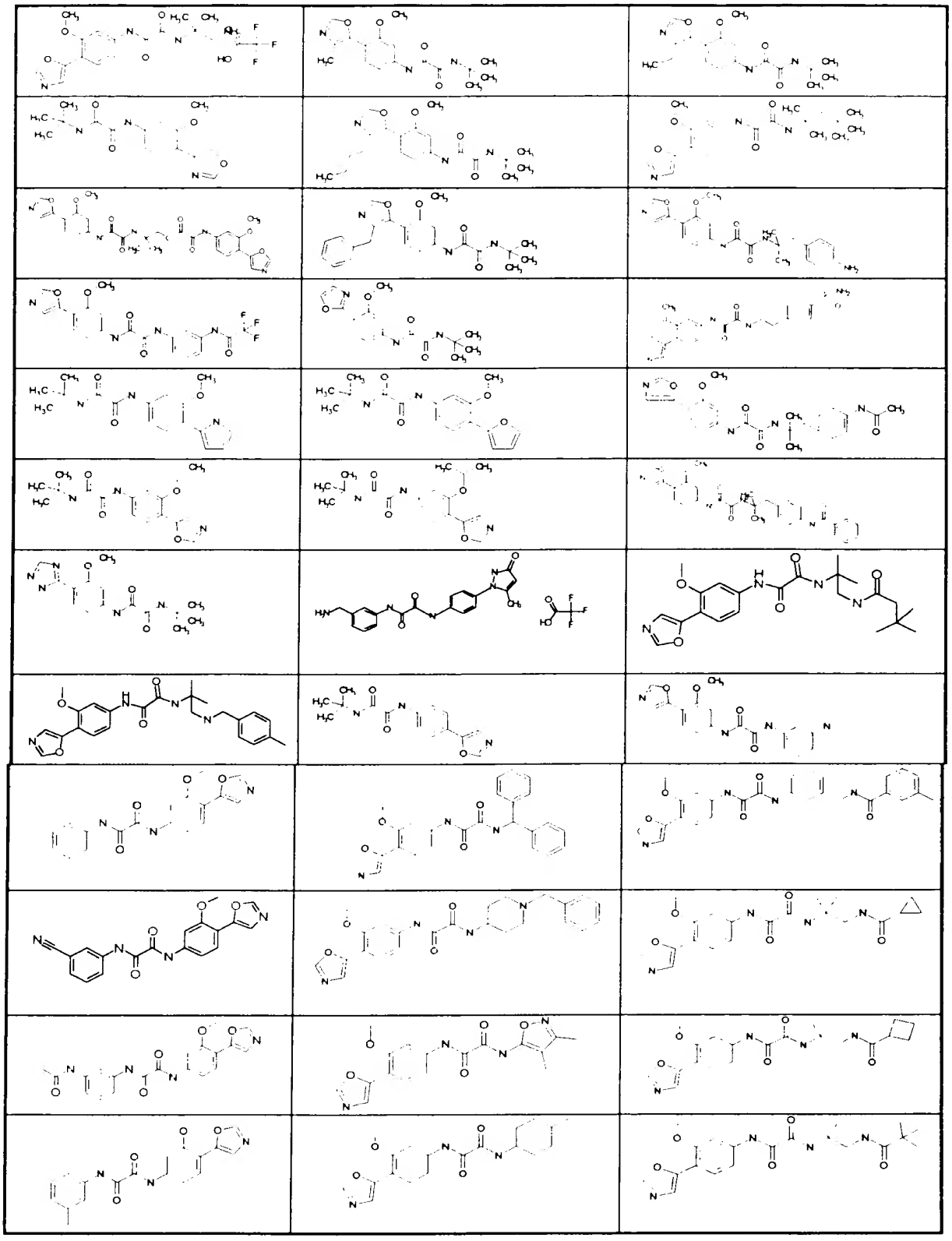
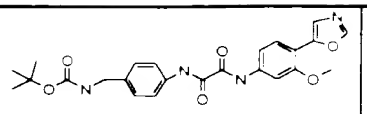
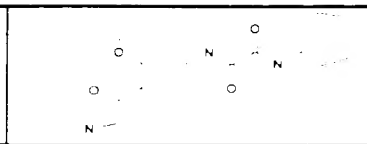
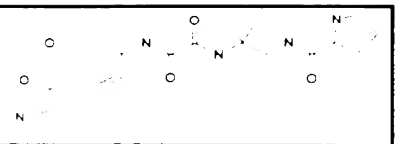
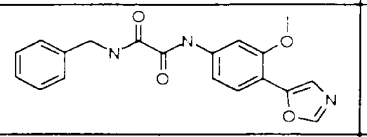
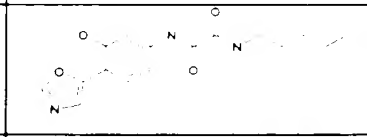
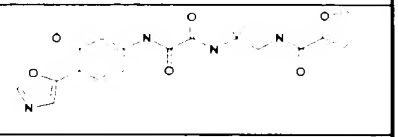
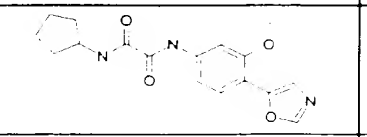
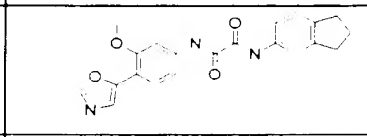
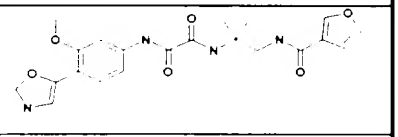
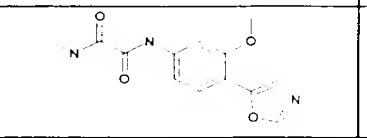
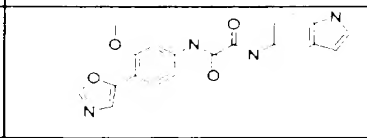
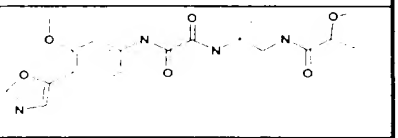
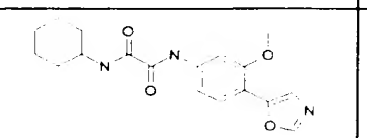
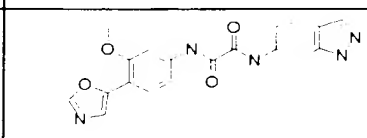
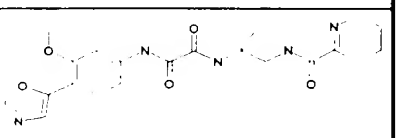
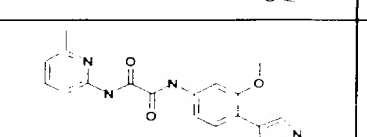
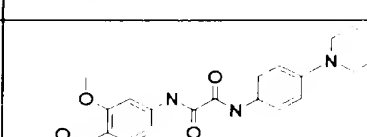
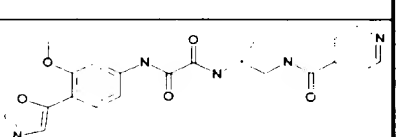
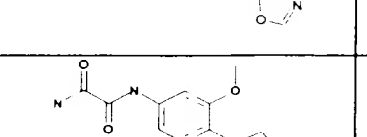
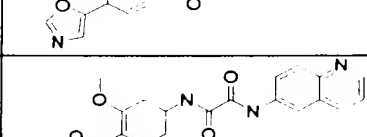
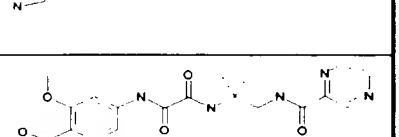
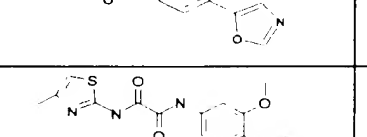
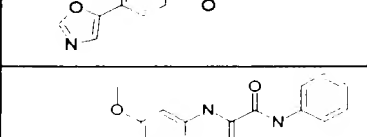
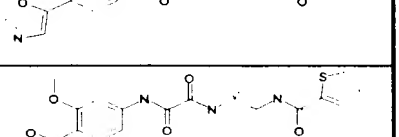
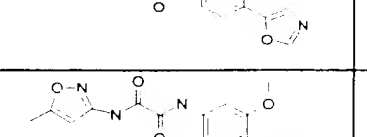
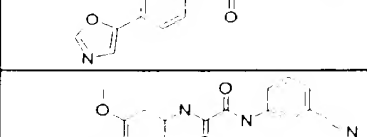
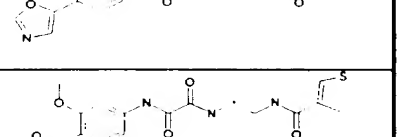
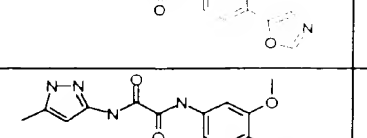
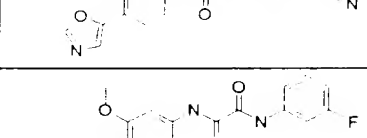
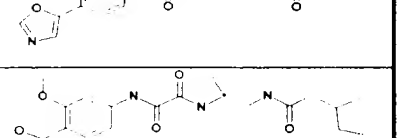
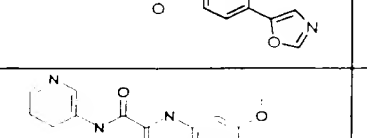
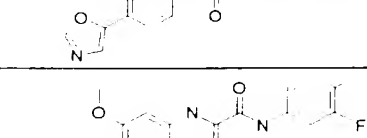
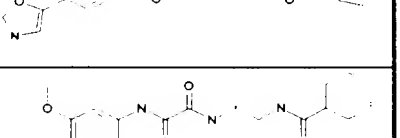
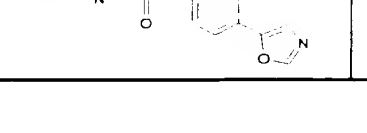
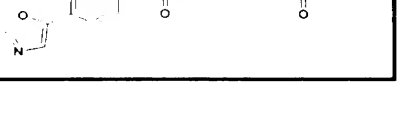
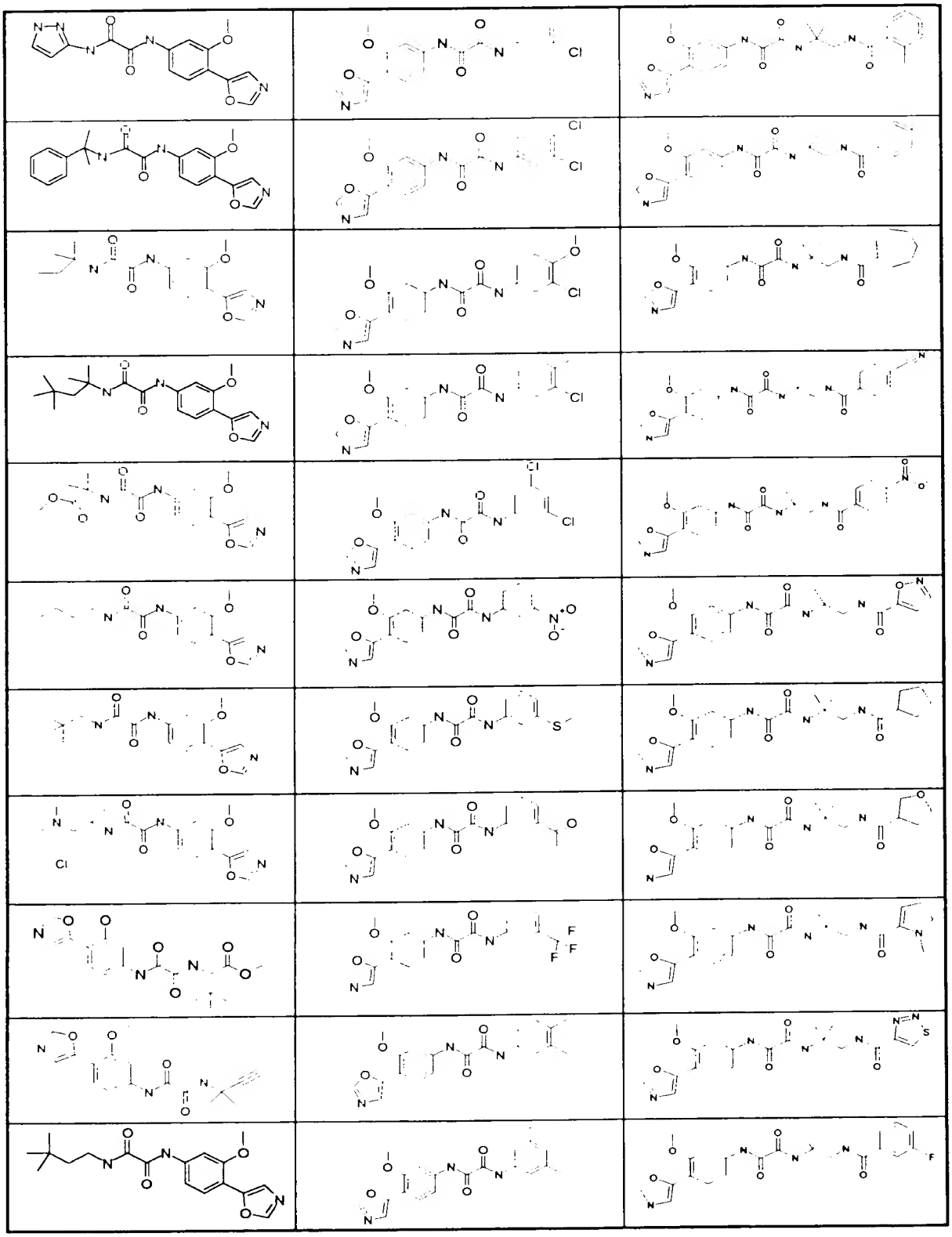
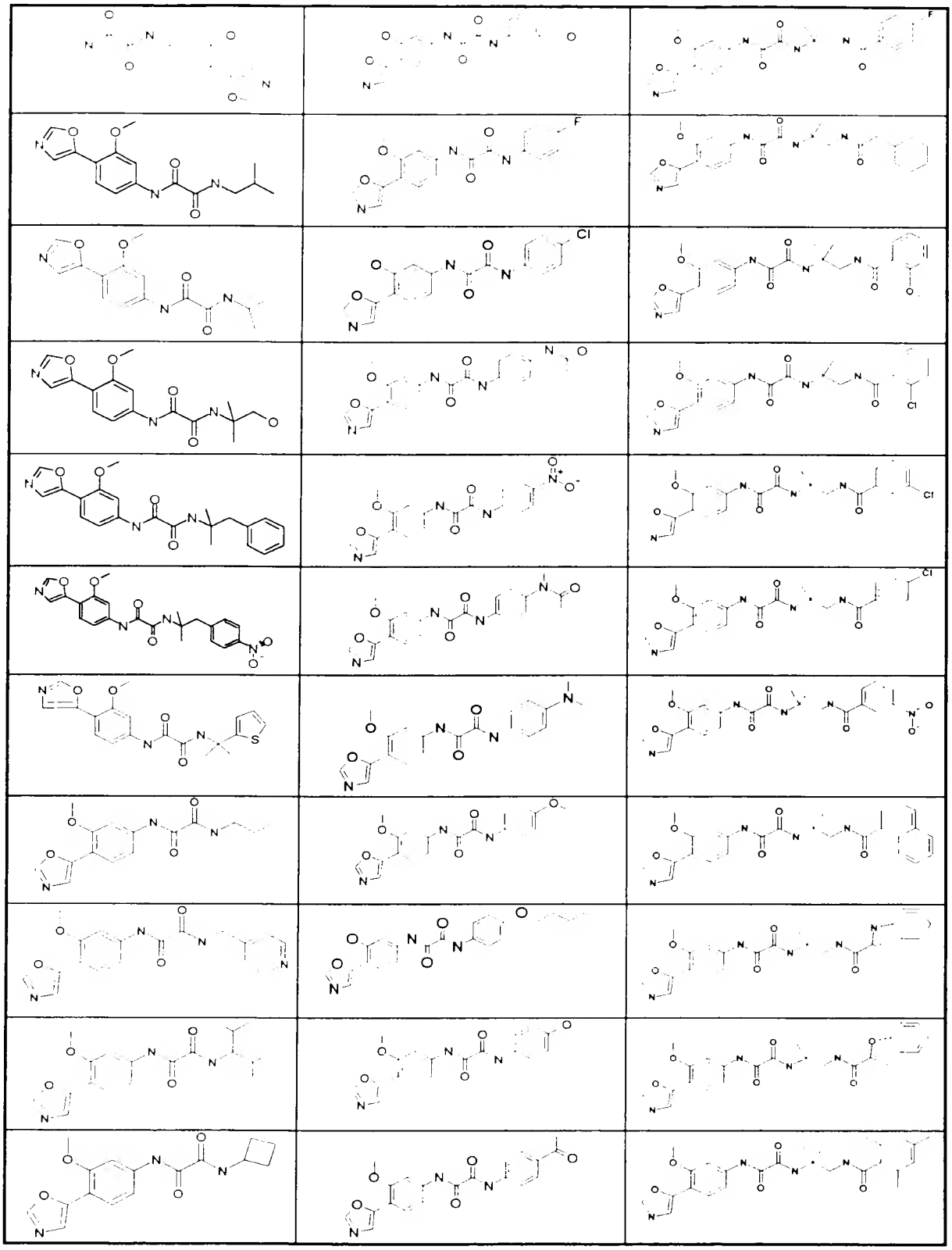
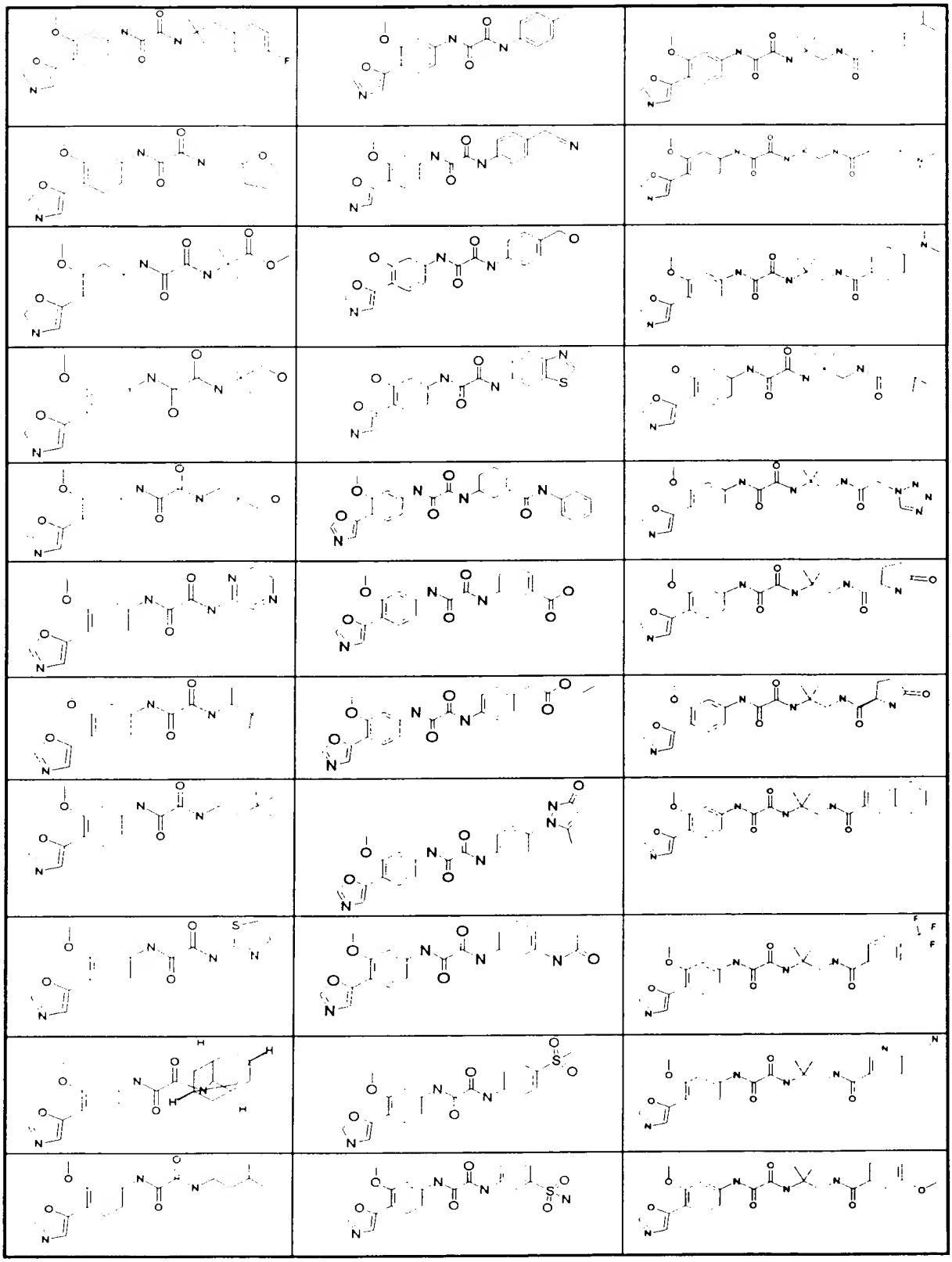
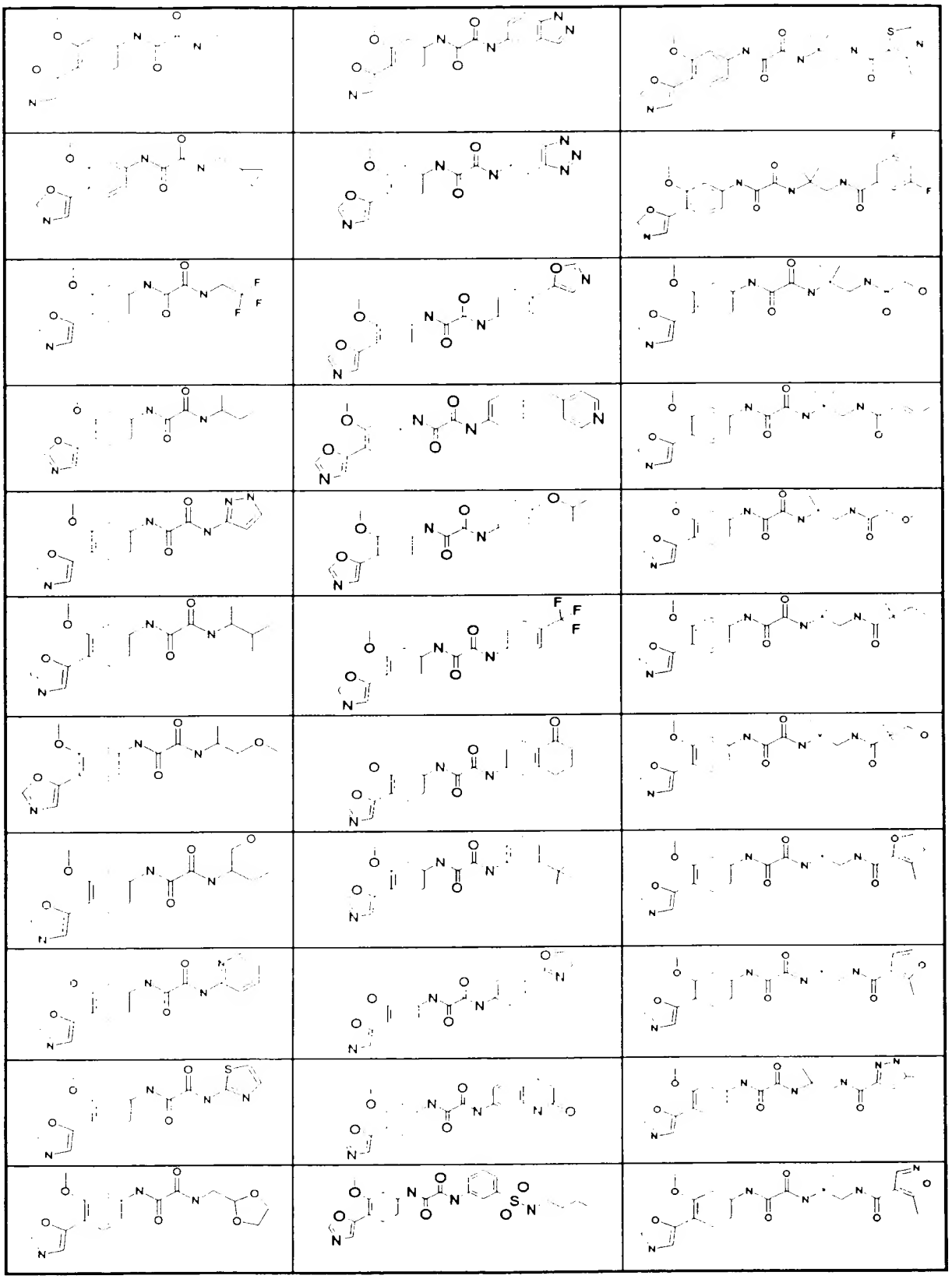


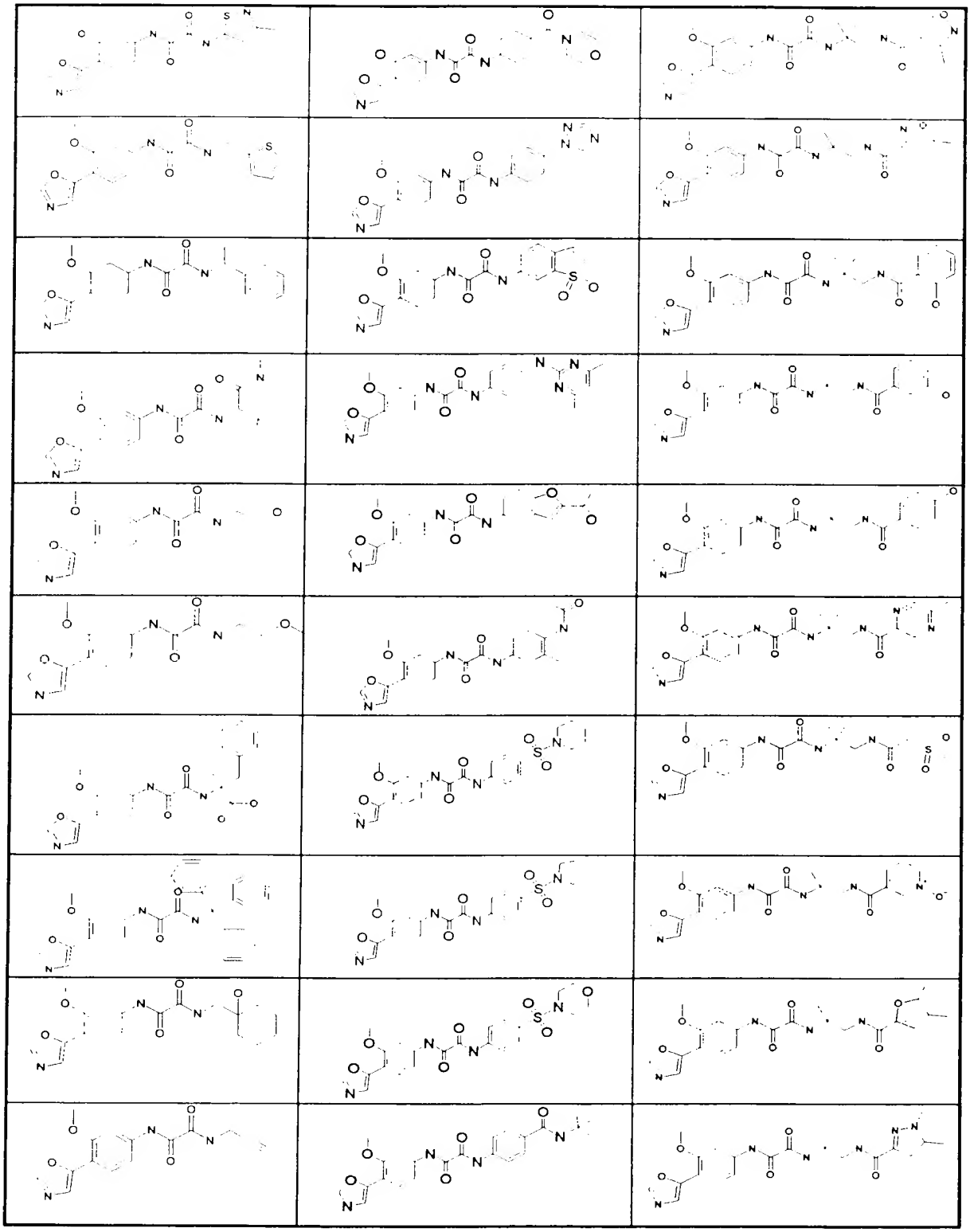
		
		
		
		
		
		
		
		
		
		
		
		

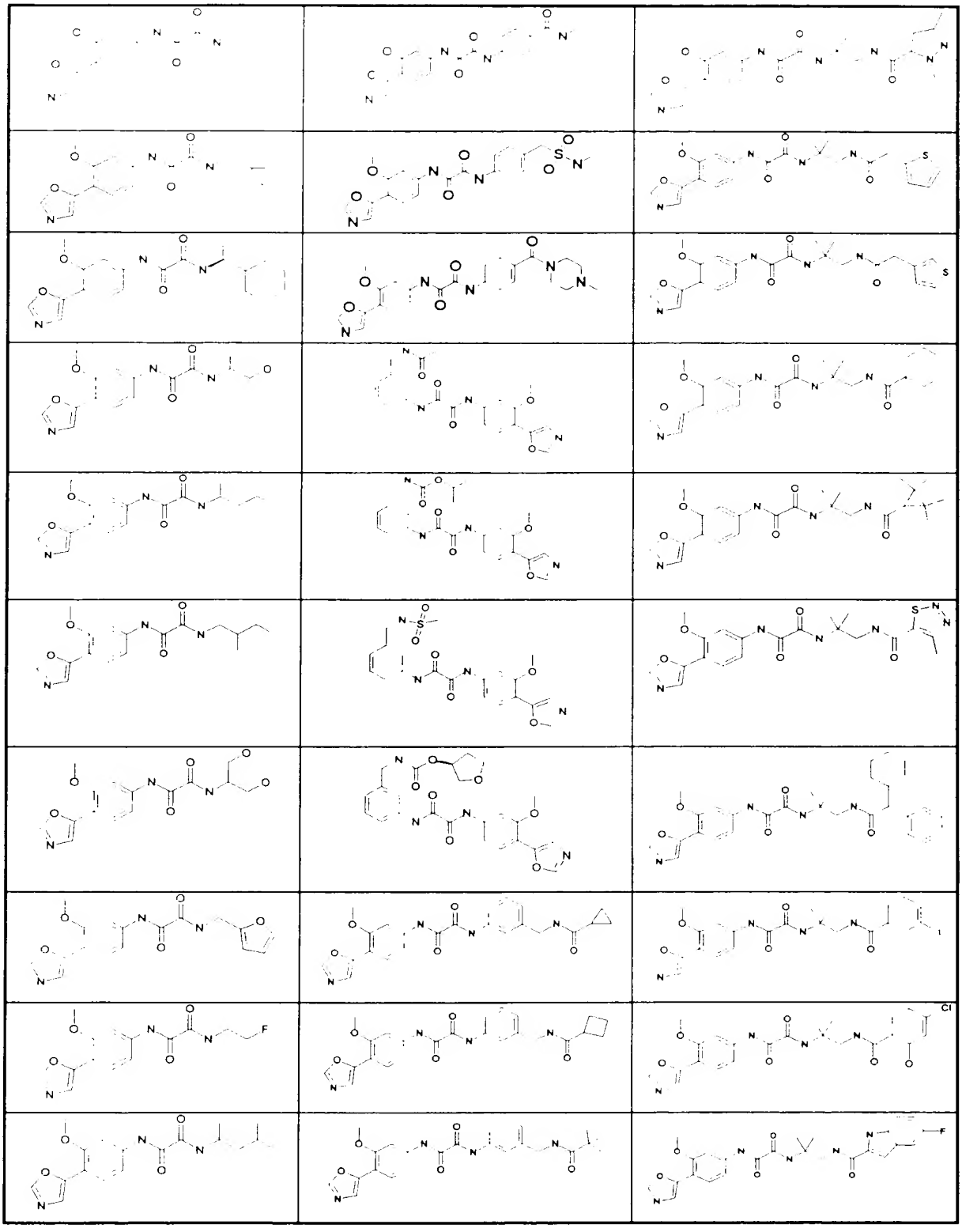


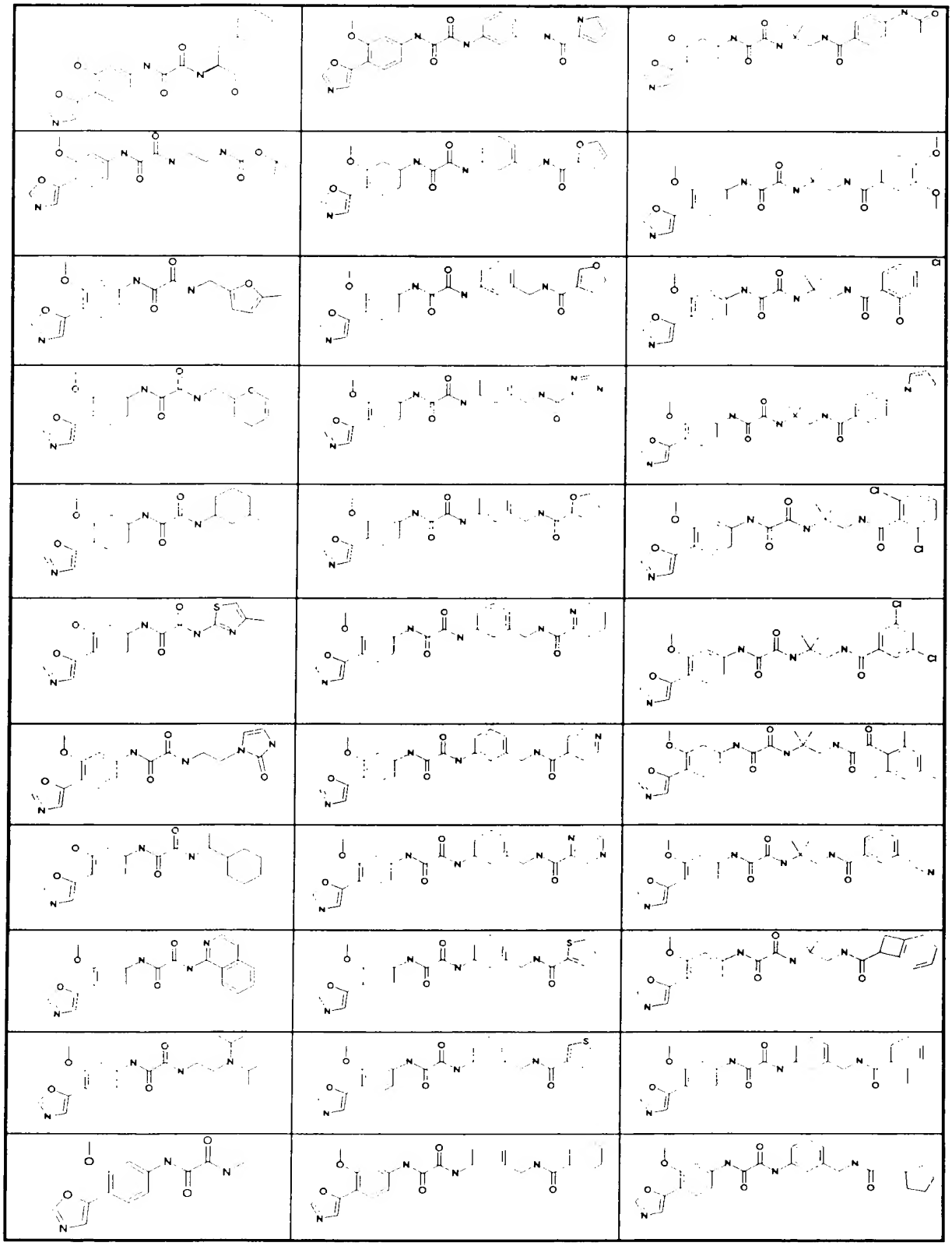


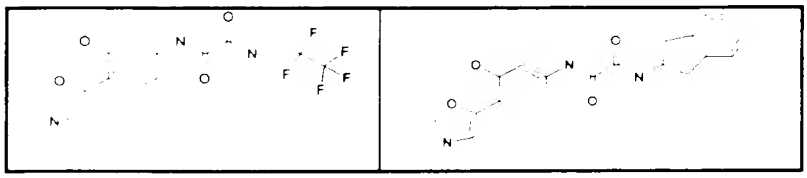








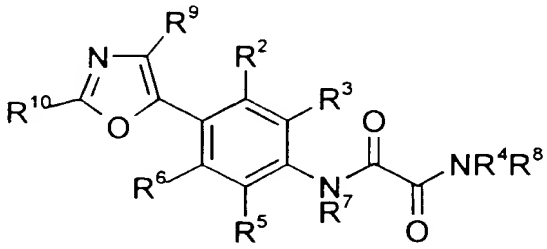




Preferred compounds of formula (I) are those where at least one of R^2, R^3, R^5 and R^6 is not hydrogen.

Furthermore, preferred compounds of formula (I) are those where R^1 represents an optionally substituted oxazole ring.

In particular, preferred compounds of formula (I) are those according to the general formula:



(IX)

wherein

R^2 to R^8 are defined as above; and,

R^9 is hydrogen, lower alkyl, aryl-lower alkyl;

R^{10} is hydrogen.

More particularly, preferred compounds of formula (I) are those according to the general formula (IX), wherein

R^2 is methoxy or chloro;

R^3 is hydrogen;

R^4 is heterocyclyl, aryl, or optionally substituted branched chain lower alkyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

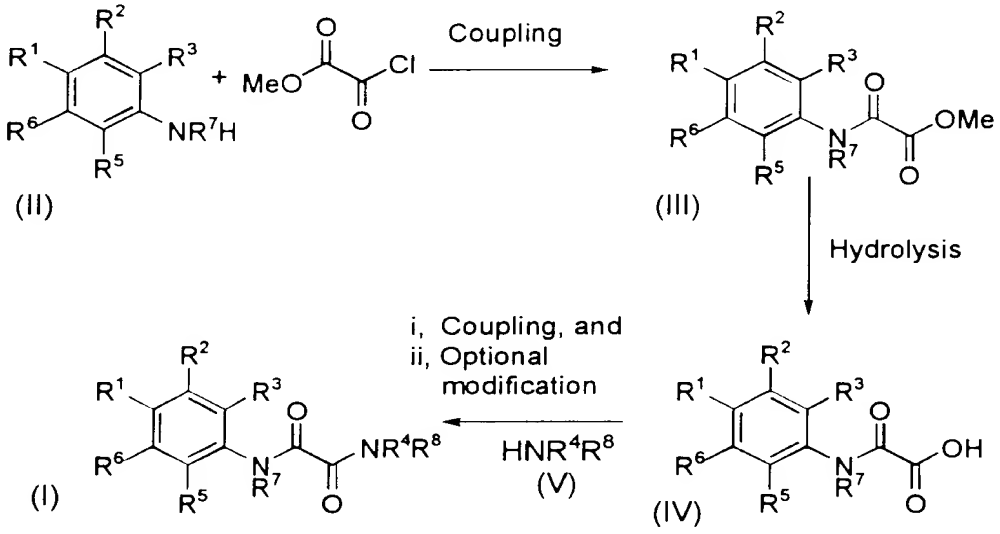
R^8 is hydrogen;

R^9 is hydrogen;

R^{10} is hydrogen.

The compounds of formula (IV) and (VIII) which are intermediates in the foregoing processes are novel and are also provided by the present invention.

Reaction Scheme A



With reference to Reaction Scheme A, the first step comprises the coupling of a compound of formula (II) with an activated oxalyl derivative, such as methyl chlorooxoacetate, to give a compound of formula (III). The reaction may be carried out in a conventional manner, suitably in an organic solvent which is inert under the reaction conditions and in the presence of an organic base at about 0°C to about room temperature. Suitable solvents include halogenated hydrocarbons, e.g. dichloromethane. Pyridine and tri(lower alkyl)amines, e.g. triethylamine, can be mentioned as examples of suitable organic bases which can be used.

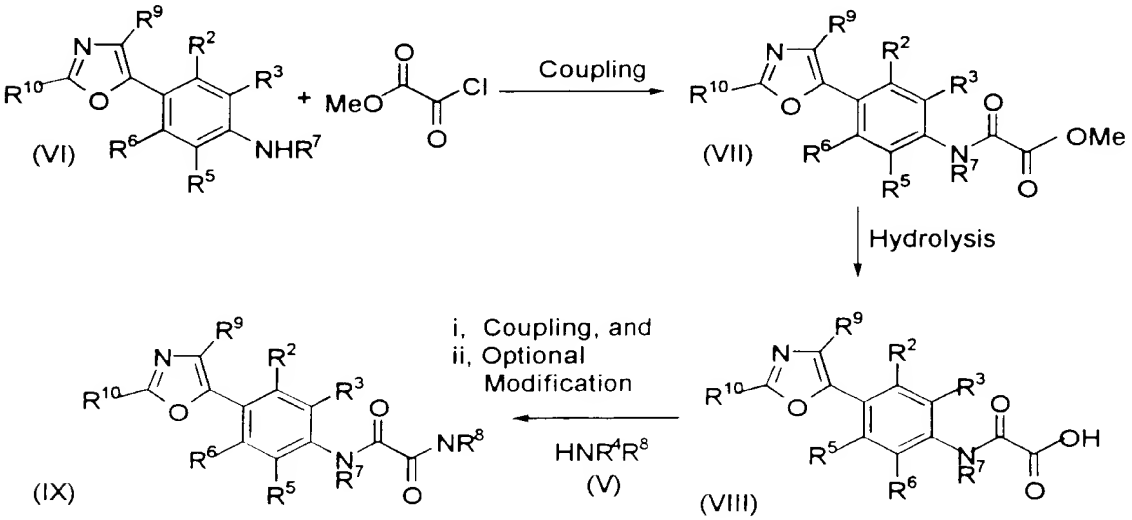
Subsequent hydrolysis of the compound of formula (III) to give the acid compound of formula (IV) may be carried out by treatment with a solution of an alkali metal hydroxide, such as sodium hydroxide, in a suitable solvent system, such as aqueous methanol.

Alternatively, a compound of formula (II) may be coupled with tert.butyl chlorooxoacetate, followed by treatment with acid to remove the tert.butyl group, to give a compound of formula (IV).

The compound of formula (IV) is then coupled with an amine compound of formula (V) using standard peptide coupling reagents, such as hydroxybenzotriazole in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, to give the oxamide compound of formula (I).

After this coupling step, the R groups of the resulting compound may be further modified by techniques known in the art, for example, functional groups may be altered, and/or connected to further groups

Reaction Scheme B



Referring to Reaction Scheme B, the first step comprises the coupling of a compound of formula (VI) with an activated oxalyl derivative, such as methyl chlorooxoacetate, to give a compound of formula (VII). The reaction is carried out in the manner described above for the formation of a compound of formula (III) from a compound of formula (II).

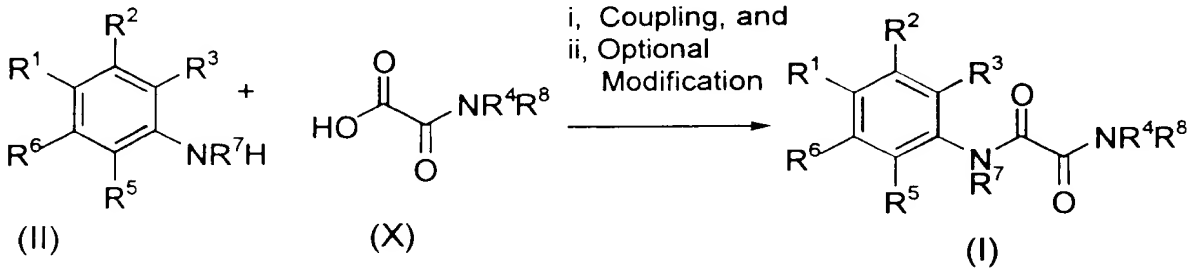
Subsequent hydrolysis of the compound of formula (VII) to give the acid compound of formula (VIII) is then carried out as described above for the hydrolysis of a compound of formula (III).

Alternatively, a compound of formula (VI) may be coupled with tert.butyl chlorooxoacetate, followed by treatment with acid to remove the tert.butyl group, to give a compound of formula (VIII).

The compound of formula (VIII) is then coupled with an amine compound of formula (V) to give the oxamide compound of formula (IX), under the conditions described above for the coupling of a compound of formula (IV) with a compound of formula (V).

After this coupling step, the R groups of the resulting compound may be further modified by techniques known in the art, for example, functional groups may be altered, and/or connected to further groups

Reaction Scheme C



Alternatively, compounds of formula (I) are made by the coupling of a compound of formula (II) with an oxalamic acid compound of formula (X), using standard peptide coupling reagents, such as hydroxybenzotriazole in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, to give the oxamide compound of formula (I).

After this coupling step, the R groups of the resulting compound may be further modified by techniques known in the art, for example, functional groups may be altered, and/or connected to further groups

As mentioned above, the compounds of formula (I) and salts thereof are inhibitors of IMPDH enzyme both in vitro and in vivo, and can be used in the control or prevention of IMPDH mediated conditions or diseases.

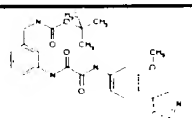
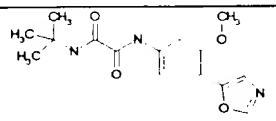
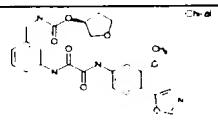
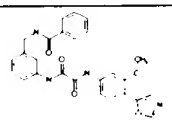
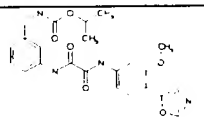
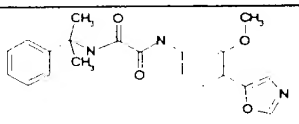
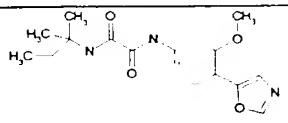
IMPDH activity can be assayed using an adaptation of the method reported by Carr [S. Carr et al., J. Biol. Chem. 268, p.27286 (1993)], the disclosure of which is herein incorporated by reference. IMPDH activity was measured spectrophotometrically, by monitoring the increase in absorbance at 340nm due to the formation of NADH (ε340 is 6220 M-1 cm-1) from the reduction of NAD. The IMPDH reaction mixture contained 0.1M Tris pH8.0, 0.1M KCl, 1mM DTT, 3mM EDTA, 100mM IMP and 100mM NAD. The reaction was initiated by the addition of IMPDH (human type II) to a final concentration in the assay of between 1nM and 5nM with respect to the IMPDH tetramer. The initial rate is measured by following the linear increase in absorbance at 340nm at 37°C for 45 minutes. The reading was conducted using a Spectromax 190 (Molecular Devices) spectrophotometer in a 96 well plate format with a final reaction volume of 200µl.

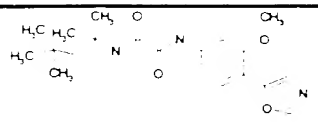
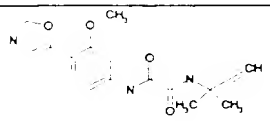
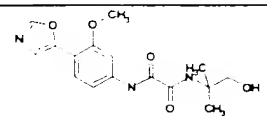
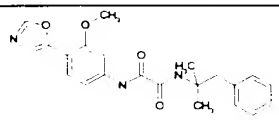
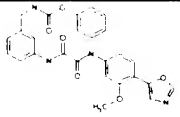
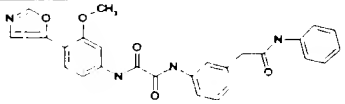
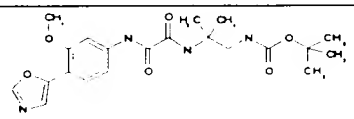
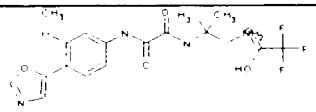
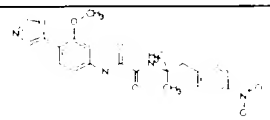
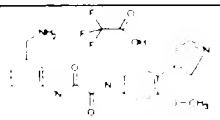
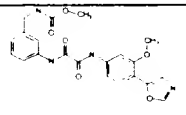
For inhibitor assay analysis, the compound is dissolved in DMSO to a final concentration of 10mM and added to the initial reaction mixture as 5µl to give final DMSO concentration of 2.5%. The enzyme reaction is initiated by the addition of IMPDH and the initial rates measured as above. IC_{50} determinations are made by measuring the initial rates in the presence of 10 concentrations of inhibitor and fitting the data using the 4 parameter curve fit from the Softmax pro software (Molecular Devices).

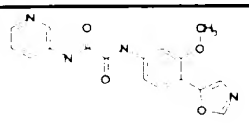
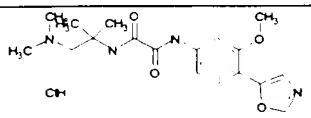
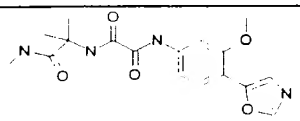
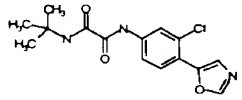
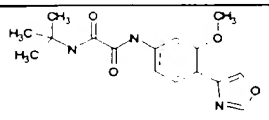
Preferred compounds of the invention tested in the above assay have an IC_{50} value up to 500nM i.e. 0.5 μM.

Specific examples of IC_{50} values for preferred compounds of formula (I) are set out below in Table 2:

Table 2

Compound of Formula (I)		IC_{50} (μM)
	tert-Butyl [3-[[[3-methoxy-4-(5-oxazolyl) anilino]oxalyl]amino]benzyl]carbamate	0.036
	N-tert-Butyl-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide	0.037
	[3-[[[3-Methoxy-4-(5-oxazolyl)anilino] oxalyl]amino]benzyl]carbamic acid tetrahydro-3(S)-furyl ester	0.044
	N-[3-(Benzamidomethyl)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide	0.013
	Isopropyl [3-[[[3-methoxy-4-(5-oxazolyl) anilino]oxalyl]amino]benzyl]carbamate	0.033
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-(1-methyl-1-phenylethyl)oxalamide	0.03
	N-(1,1-Dimethylpropyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide	0.031

	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-(1,1,3,3-tetramethyl-butyl)oxalamide	0.034
	N-(1,1-Dimethylpropargyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide	0.048
	N-(2-Hydroxy-1,1-dimethylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide	0.072
	N-(1,1-Dimethyl-2-phenylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide	0.015
	Phenyl [3-[[[4-(5-oxazolyl)anilino] oxalyl]amino]benzyl]carbamate	0.011
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[3-[(phenylcarbamoyl)methyl] phenyl]oxalamide	0.035
	tert-Butyl [2-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropyl]carbamate	0.075
	N-(2-Amino-1,1-dimethylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate (1:1)	0.097
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[1,1-dimethyl-2-(4-nitrophenyl) ethyl]oxalamide	0.010
	N-[3-(Aminomethyl)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate (1:1)	0.233
	Methyl [3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate	0.121

	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-(3-pyridyl)oxalamide	0.277
	N-[3-[(Benzenesulfonamido)methyl]phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide	0.125
	N-(2-Dimethylamino-1,1-dimethylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide hydrochloride (1:1)	0.17
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[1-methyl-1-(methylcarbamoyl)ethyl]oxalamide	0.199
	N-tert-Butyl-N'-[3-chloro-4-(5-oxazolyl)phenyl]oxalamide	0.169
	N-tert-Butyl-N'-[3-methoxy-4-(4-oxazolyl)phenyl]oxalamide	0.46

Compounds of formula (I) which are acidic can form pharmaceutically acceptable salts with bases such as alkali metal hydroxides, e.g. sodium hydroxide and potassium hydroxide; alkaline earth metal hydroxides, e.g. calcium hydroxide, barium hydroxide and magnesium hydroxide, and the like; with organic bases e.g. N-ethyl piperidine, dibenzylamine, and the like. Those compounds of formula (I) which are basic can form pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric acid and hydrobromic acid, sulphuric acid, nitric acid and phosphoric acid, and the like, and with organic acids, e.g. with acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid and p-toluene sulphonic acid, and the like. The formation and isolation of such salts can be carried out according to methods known in the art.

The oxamide derivatives provided by the present invention (i.e. the compounds of formula (I) and their pharmaceutically acceptable salts), can be used as medicaments, for example in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered enterally, such as orally, in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, or nasally, e.g. in the form of nasal sprays. They can also be administered rectally, e.g. in the form of suppositories, or parenterally, (e.g. intramuscularly, intravenously, or subcutaneously), for example, in the form of injection solutions.

For the manufacture of pharmaceutical preparations the oxamide derivatives can be formulated with therapeutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active ingredient no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water, polyols, sucrose, saccharose, invert sugar, glucose and the like. Suitable carriers for the manufacture of injection solutions are, for example, water, saline, alcohols, polyols, glycerine, vegetable oils and the like. Natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like are suitable carriers for the manufacture of suppositories. The pharmaceutical preparations of the present invention may also be provided as sustained release formulations or other appropriate formulations.

The pharmaceutical preparations can also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colourants, flavourants, salts for adjustment of the osmotic pressure, buffers, masking agents or antioxidants. They may also contain other therapeutically active substances, such as an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-parasitic agent, an anti-fungal agent, an anti-inflammatory agent and/or an anti-vascular hyperproliferation

agent. A preferred agent that may be used with the compounds of the present invention is interferon or derivatives thereof, such as conjugates with polyethylene glycol.

Medicaments containing compounds of formula (I) or salts thereof and a therapeutically acceptable carrier, as well as a process for the manufacture of such medicaments are also objects of the present invention. This process comprises bringing a compound of formula (I) or a pharmaceutically acceptable salt thereof into a galenical administration form together with a therapeutically inert carrier material and, if desired, one or more additional therapeutically active substances.

A further object of the invention comprises the use of the oxamide derivatives provided by the invention in the treatment of an immune mediated condition or disease, a viral disease, a bacterial disease, a parasitic disease, inflammation, an inflammatory disease, a hyperproliferative vascular disease, a tumour, or cancer. The dosage can vary within wide limits and will, of course, be adjusted to the individual requirements in each particular case. Dosage levels of between about 0.01 and about 100 mg/kg body weight per day (preferably 0.5 - 75 mg/kg/day) in monotherapy and/or in combination therapy are preferred, administered from about 1 -5 times per day. The active ingredient may be combined with a carrier material. A typical preparation will contain from about 5% - 95% active compound (w/w) (preferably from about 20% - 80% active compound). The daily dosage can be administered as a single dosage or in divided dosages.

The compounds and compositions of the present invention may be for use in monotherapy and/or combination therapy, i.e. the treatment may be in conjunction with the administration of one or more additional therapeutically active substance(s). When the treatment is combination therapy, such adminstration may be concurrent or sequential with respect to that of the oxamide derivatives of the present invention. Thus, concurrent administration, as used herein, includes administration of the agents in conjunction or combination, together, or before or after each other.

It will be understood that references herein to treatment extend to prophylaxis as well as to treatment of existing conditions. Treatment of a disease or condition, as used herein,

also includes preventing, inhibiting, regressing, reversing, alleviating or relieving the disease or condition, or the clinical symptoms thereof. The term "subject" as used herein refers to animals, including humans and other mammals.

The following Examples illustrate the present invention.

With regard to the starting materials that are known compounds some of these may be purchased from commercial suppliers. Other starting materials that are known and their analogues can be prepared by methods well known in the art. Examples of compounds available from commercial suppliers, and citations to the synthesis of other compounds and their analogues are provided in the following:

Compounds of formula (II) and the compounds of formula (VI) are obtained from commercial suppliers (e.g. 4-(5-oxazolyl)aniline, Maybridge catalogue number DFP 00120), or prepared by adaptation of the methods disclosed in published patent application WO 974002, or prepared by adaptation of the methods provided in Palacz et al., FEBS Lett., 1984, 176(2), 365-370.

The compounds of formula (V) are obtained from commercial suppliers (e.g. tert-butylamine, Aldrich catalogue number B8,920-5; Cumylamine, TCI-US catalogue number C1293), or prepared by adaptation of the methods provided in Kazuo Achiwa et al., Chem.Pharm.Bull., 1998, 46(4), 697-670.

The compounds of formula (X) are prepared by adaptation of the methods provided in Minisci et al., J. Org. Chem., 1995, 60(17), 5430-5433.

Examples of commercially available reagents include those used in Examples 7, 10 and 11, (2-methoxy-4-nitrobenzoic acid, Aldrich catalogue number 42,291-6; tert-butylacetic acid, Aldrich catalogue number B8,840-3; and p-tolualdehyde, Aldrich catalogue number T3,560-2, respectively).

Where indicated, the NMR spectra were recorded on a Bruker DRX 400 MHz

spectrometer with the probe temperature set at 300 K.

Where indicated by "(M+;EI)", mass spectra were recorded under electron impact conditions (EI), on a THERMOQUEST MAT95 S with a source temperature of 200°C. Other mass spectra were recorded under electrospray ionisation spectra (ESI) conditions, on one of the following machines:

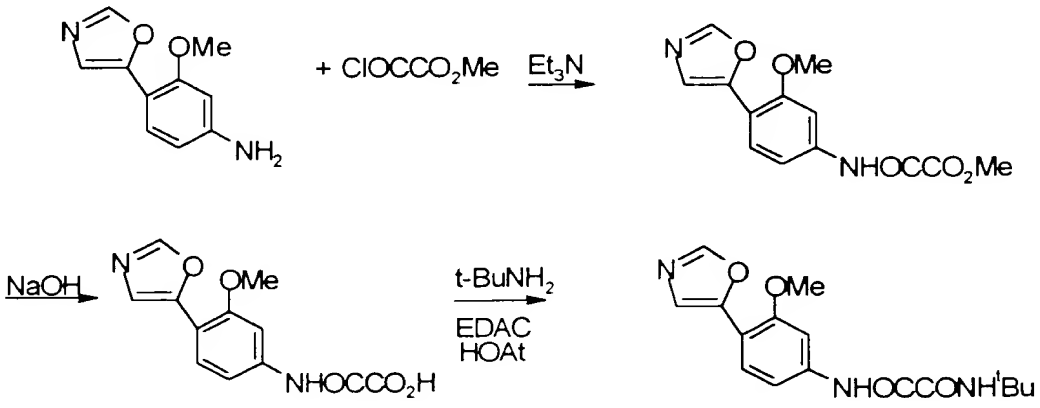
a) THERMOQUEST SSQ 7000 [Solvent 0.085% TFA in 90% Acetonitrile/water; flow rate 100 microliters/minute; capillary 250°C; spray voltage 5KV; sheath gas 80 psi], or

b) LC-MS system (liquid chromatograph coupled to mass spectrum) THERMOQUEST TSQ 7000 ELECTROSPRAY or MICROMASS PLATFORM ELECTROSPRAY [Solvent 0.1% TFA in water or 0.085% TFA in 90% acetonitrile/ water or 0.085% TFA in acetonitrile].

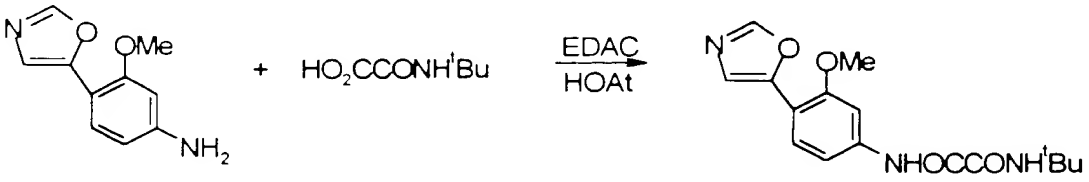
Unless otherwise indicated, the mass spectroscopy values recorded in the MS(ES) column refer to $(M+H)^+$ values, apart from the ones shown as $(M^+;EI)$.

Example 1

N-Tert-butyl-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide



Example 1, Alternative synthesis



A solution of 26 mg (0.1 mmol) of N-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamic acid, 15 mg (0.2 mmol) of tertiary butylamine, 28 mg (0.15 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 15 mg (0.11 mmol) of 1-hydroxy-7-azabenzotriazole in 1 ml of dimethylformamide was stirred at room temperature for 4 hours then diluted with ethyl acetate and washed with 2M hydrochloric acid, saturated sodium bicarbonate and water. The resulting solution was dried over magnesium sulphate and evaporated to dryness. The residue was triturated with diethyl ether/petrol (1:1) and collected by filtration to give 11 mg of N-tert-butyl-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide as a white solid. MS: m/e 318.0 $[M+H]^+$.

The starting material was prepared as follows:

i) 5.7 g (30 mmol) of 3-methoxy-4-(5-oxazolyl)aniline and 3.33 g (33 mmol) of triethylamine were dissolved in 50 ml of dichloromethane and the solution was cooled to 0°C. A solution of 3.86 g (31.5 mmol) of methyl oxalyl chloride in 10 ml of dichloromethane was added dropwise and the resulting mixture was stirred for 1 hour then washed with 2M hydrochloric acid. The precipitated solid was collected by filtration and washed with dichloromethane and water to give 6.2 of methyl N-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamate as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.88 (3H,s), 3.94 (3H,s), 7.48 (1H,s), 7.58 (1H,dd), 7.65 (1H,d), 7.68 (1H,d)), 8.39 (1H,s), 10.92 (1H,s).

ii) 6.2 g (22.46 mmol) of methyl N-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamate and 1.2 g (30 mmol) of sodium hydroxide were refluxed in 240 ml of methanol/water

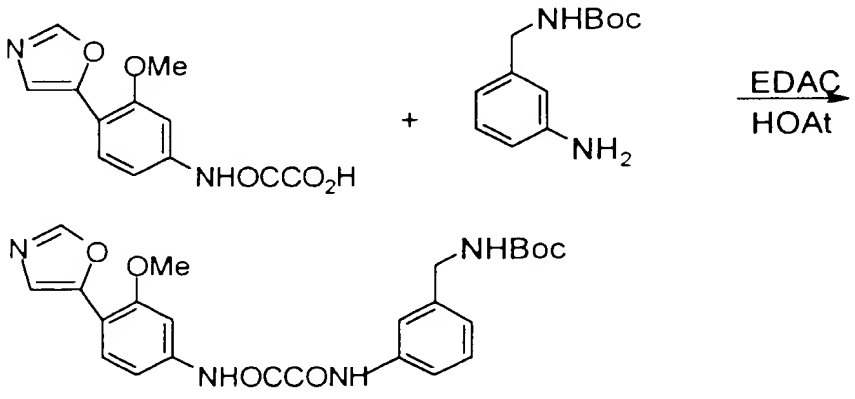
(1:1) for 2 hours then cooled, filtered and acidified with 2M hydrochloric acid. The precipitated solid was collected by filtration and washed with water, acetone and diethyl ether to give 5.1 g of N-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamic acid as a pale yellow solid. MS: m/e 262.9 $[M+H]^+$.

Alternatively N-tert-butyl-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide can be prepared as follows:

A solution of 95 mg (0.5 mmol) of 3-methoxy-4-(5-oxazolyl)aniline, 73 mg (0.5 mmol) of N-tert-butyloxalamic acid, 134 mg (0.7 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 75 mg (0.55 mmol) of 1-hydroxy-7-azabenzotriazole in 4 ml of dichloromethane was stirred a room temperature for 18 hours. The resulting mixture was washed with 2M hydrochloric acid and saturated sodium bicarbonate, dried over magnesium sulphate and evaporated to dryness. The residue was triturated with petrol and collected by filtration to give 128 mg of N-tert-butyl-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide as a pale yellow solid. MS: 318 $[M+H]^+$.

Example 2

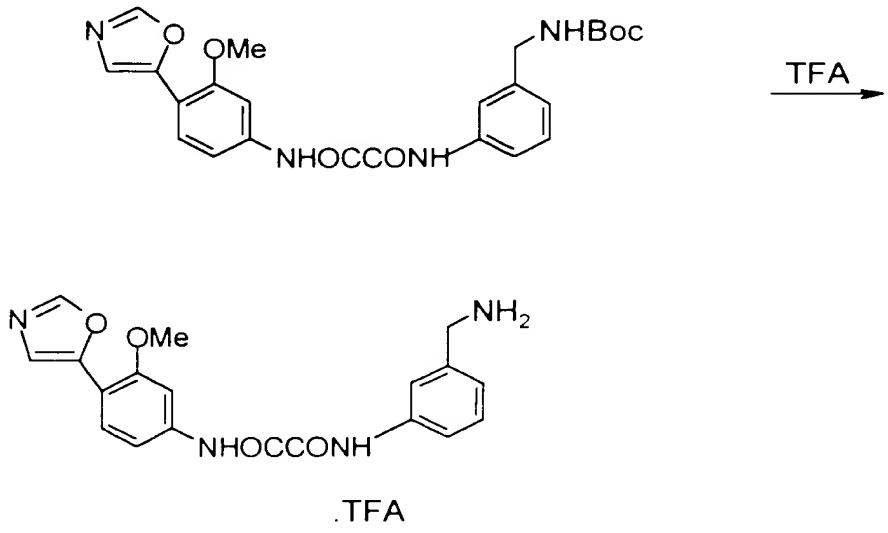
Tert-butyl [3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl] amino]benzyl]carbamate



A mixture of 2.04 g (7.79 mmol) of N-(3-methoxy-4-(5-oxazolyl)phenyl]oxalamic acid, prepared as described above in Example 1 above, 1.9 g (8.56 mmol) of tert-butyl (3-aminobenzyl)carbamate, 1.8 g (9.4 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1.3 g (9.6 mmol) of 1-hydroxy-7-azabenzotriazole in 30 ml of dimethylformamide was stirred for 20 hours at room temperature. The resulting precipitate was collected by filtration and washed with dichloromethane to give 1.8 g of tert-butyl [3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate as a white solid. MS: m/e 466 M^+.

Example 3

N-[3-(Aminomethylphenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate

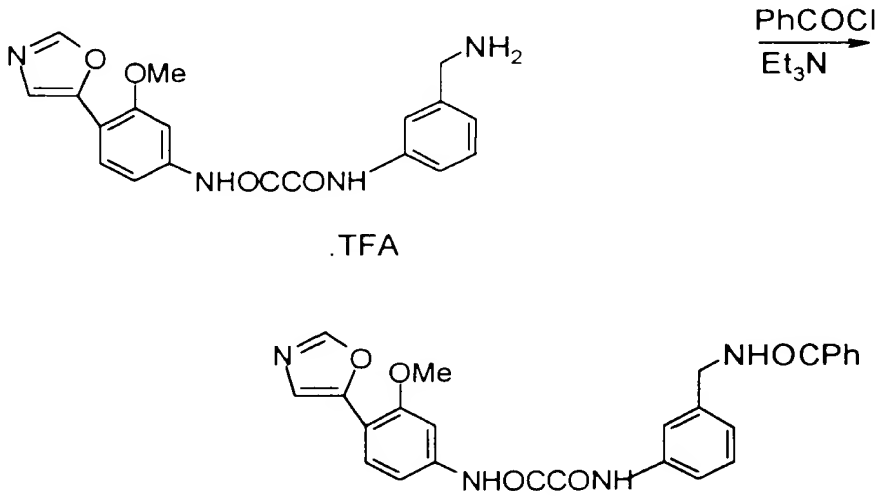


15 mg (0.032 mmol) of tert-butyl [3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate, prepared as described in Example 2 above, were dissolved in 1 ml of dichloromethane and 1 ml of trifluoroacetic acid at room temperature for 5 minutes. The solution was evaporated to dryness, the residue

triturated with diethyl ether and collected by filtration to give 11 mg of N-[3-(aminomethylphenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate as a white solid. MS: m/e 408 $[M+H+MeCN]^+$.

Example 4

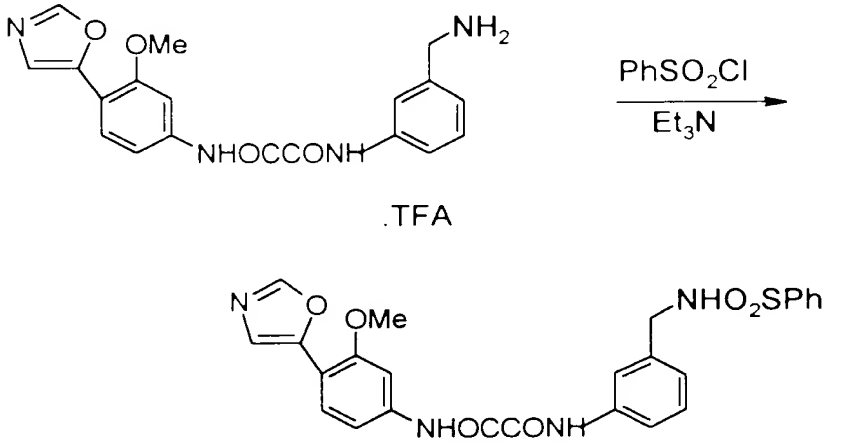
N-[3-(Benzamidomethyl)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide



29 mg (0.21 mmol) of benzoyl chloride were added to a solution of 100 mg (0.21 mmol) of N-[3-(aminomethyl)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl] oxalamide trifluoroacetate, prepared as described in Example 3 above, and 46 mg (0.46 mmol) of triethylamine in a mixture of 2 ml of dimethylformamide and 5 ml of dichloromethane, and stirred at room temperature for 18 hours. The solution was washed with 2M hydrochloric acid and saturated sodium bicarbonate then dried over magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel using ethyl acetate/petrol (2:1) for the elution. After trituration with diethyl ether there was obtained 45 mg of N-[3-(benzamidomethyl)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide as a white solid. MS: m/e 471.0 $[M+H]^+$.

Example 5

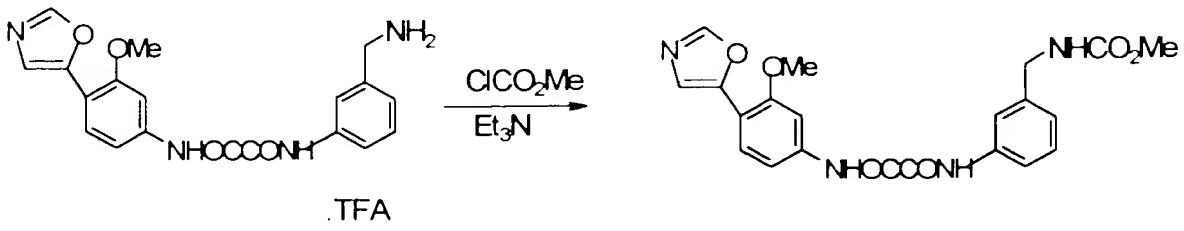
N-[3-[(Benzenesulphonamido)methyl]phenyl]-N'-[3-methoxy-4-(5-oxazolyl) phenyl]oxalamide



In an analogous manner to that described in Example 4 but replacing benzoyl chloride with phenylsulphonyl chloride there was obtained N-[3-[(benzenesulphonamido)methyl]phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide as a white solid. MS: m/e 507 $[M+H]^+$.

Example 6

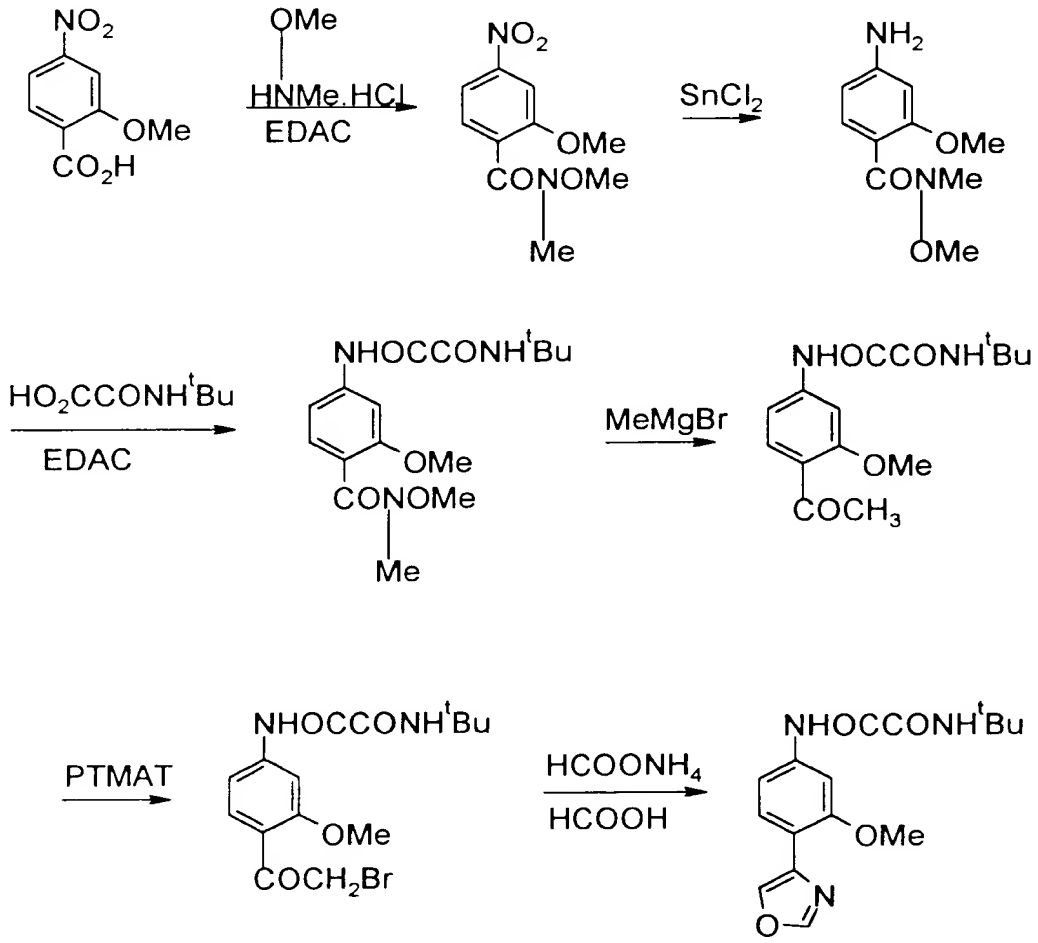
Methyl [3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxazolyl]aminobenzyl]carbamate



In an analogous manner to that described in Example 4 but replacing benzoyl chloride with methyl chloroformate there was obtained methyl [3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate as a white solid. MS: m/e 425 $[M+H]^+$.

Example 7

N-Tert-butyl-N'-[3-methoxy-4-(4-oxazolyl)phenyl]oxalamide



A mixture of 371 mg (1 mmol) of N-[4-(bromoacetyl)-3-methoxyphenyl]-N'-tert-butyloxalamide and 315 mg (5 mmol) of ammonium formate was refluxed in 10 ml of formic acid for 4 hours then cooled and evaporated to dryness. The residue was dissolved in ethyl acetate, washed with 2M sodium hydroxide and dried over magnesium sulphate. The solution was evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate/petrol (7:18) for the elution. There was obtained after trituration with diethyl ether/petrol (1:1) 65 mg of N-tert-butyl-N'-[3-methoxy-4-(4-oxazolyl)phenyl]oxalamide as a white solid. MS: m/e 318 $[M+H]^+$.

The starting material was prepared as follows:

i) A mixture of 3.94 g (20 mmol) of 2-methoxy-4-nitrobenzoic acid, 3.9 g (40 mmol) of N,O-dimethylhydroxylamine hydrochloride, 5.73 g (29.92 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.37 g (22 mmol) of 1-hydroxybenzotriazole hydrate and 5.06 g (44 mmol) of N-ethylmorpholine in 50 ml of dichloromethane was stirred at room temperature for 3 hours then washed with 2M hydrochloric acid and saturated bicarbonate. The resulting solution was dried over magnesium sulphate, evaporated to dryness and the residue triturated with diethyl ether and collected by filtration to give 3.95 g of N,O-dimethyl 2-methoxy-4-nitrobenzohydroxamate as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.37 (3H,s), 3.48 (3H,s), 3.97 (3H,s), 7.45 (1H,d), 7.80 (1H,d), 7.91 (1H,dd).

ii) A mixture of 1.2 g (5 mmol) of N,O-dimethyl 2-methoxy-4-nitrobenzohydroxamate and 4.75 g (25 mmol) of tin(II) chloride in 40 ml of ethanol was heated at 80°C for 30 minutes then cooled and evaporated to dryness. The residue was dissolved in dichloromethane, washed with 2M sodium hydroxide and the organic phase dried over magnesium sulphate and evaporated to dryness to give 960 mg of N,O-dimethyl 4-amino-2-methoxybenzohydroxamate as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.25 (3H,s), 3.62 (3H,s), 3.79 (3H,s), 6.22 (1H,d), 6.28 (1H,dd), 7.09 (1H,d).

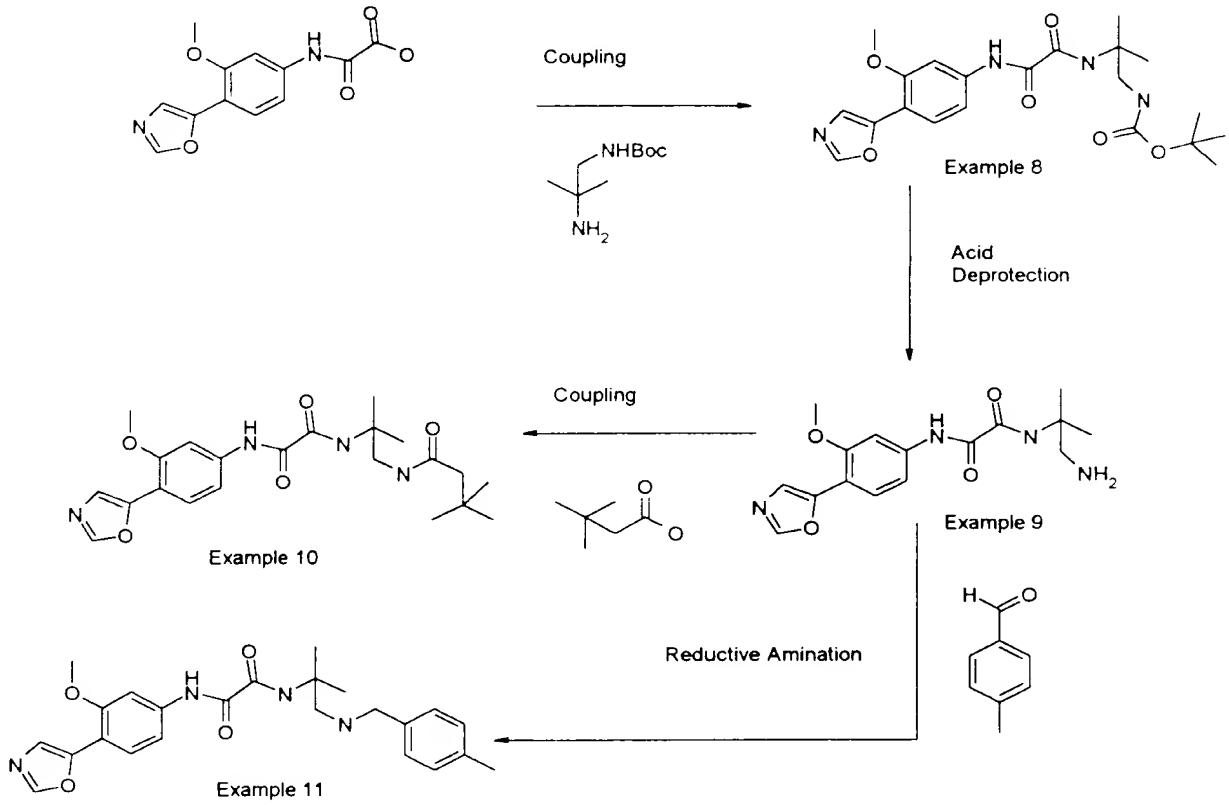
iii) A mixture of 700 mg (3.33 mmol) of N,O-dimethyl 4-amino-2-methoxybenzohydroxamate, 483 mg (3.33 mmol) of N-tert-butyloxalamic acid, 600 mg (3.92 mmol) of 1-hydroxybenzotriazole hydrate and 960 mg (5.01 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 15 ml of dichloromethane was stirred at room temperature for 3 hours then washed with 2M hydrochloric acid and saturated sodium bicarbonate. The organic phase was dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate/petrol (3:1) for the elution to give 960 mg of N,O-dimethyl 4-[[(tert-butylamino)oxalyl] amino]-2-methoxybenzohydroxamate as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (9H,s), 3.25-3.4 (3H,br.s.), 3.45-3.65 (3H,br.s.), 3.89 (3H,s), 7.08 (1H,dd), 7.29 (1H,d), 7.44 (1H,s), 7.53 (1H,d), 9.40 (1H,s).

iv) 3.1 ml (4.34 mmol) of 1.4M methylmagnesium bromide in tetrahydrofuran were added in portions over 1 hour to a solution of 337 mg (1 mmol) of N,O-dimethyl 4-[[(tert-butylamino)oxalyl]amino]-2-methoxybenzohydroxamate in 10 ml of anhydrous tetrahydrofuran. The resulting solution was diluted with diethyl ether and washed with 2M hydrochloric acid. The organic phase was dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate/petrol (3:7) for the elution to give 255 mg of N-(4-acetyl-3-methoxyphenyl)-N'-tert-butyloxalamide as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (9H,s), 2.61 (3H,s), 3.96 (3H,s), 7.03 (1H,dd), 7.43 (1H,s), 7.64 (1H,d), 7.82 (1H,d), 9.47 (1H,s).

v) 320 mg (0.85 mmol) of phenyltrimethylammonium tribromide were added in portions over 10 minutes to a stirred solution of 247 mg (0.85 mmol) of N-(4-acetyl-3-methoxyphenyl)-N'-tert-butyloxalamide in 5 ml of anhydrous tetrahydrofuran. After 15 minutes a further 100 mg (0.26 mmol) of phenyltrimethylammonium tribromide were added. The resulting suspension was diluted with diethyl ether, washed with water and the organic phase was dried over magnesium sulphate. Evaporation gave a gum which was chromatographed on silica gel using firstly 0.5% methanol in dichloromethane then 1% methanol in dichloromethane for the elution. The product was dissolved in diethyl ether/petrol (2:1) and the resulting crystals were collected by

filtration to give 135 mg of N-[4-(bromoacetyl)-3-methoxyphenyl]-N'-tert-butyloxalamide as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (9H,s), 3.99 (3H,s), 4.61 (2H,s), 7.06 (1H,dd), 7.42 (1H,s), 7.68 (1H,d), 7.93 (1H,d), 9.51 (1H,s).

Examples 8-11



Example 8

Tert-butyl[2-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropyl]carbamate

77mg (0.87 mmol) of tert-butyl (2-amino-2-methylpropyl)carbamate , 207 mg (1.05 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 166 mg (1.08 mmol) of 1-hydroxy-7-azabenzotriazole and 200 mg (0.76 mmol) of N-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamic acid were dissolved in 5 ml of dichloromethane

and 5 ml of dimethylformamide and stirred for 16 hours at room temperature. The mixture was then diluted with 50 ml of dichloromethane and washed with a 10% solution of citric acid and brine. The organic layer was then dried with anhydrous magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel using 30% ethyl acetate in hexane for the elution to give 165 mg of tert-butyl [2-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropyl]carbamate as a yellow solid, ^{1}H NMR (400MHz, d6 DMSO) δ: 1.35 (s, 6H), 1.45 (s, 9H), 3.25 (d, 2H), 3.95 (s, 3H), 7.25 (t, 1H), 7.55 (s,1H), 7.70 (m, 2H), 7.80 (s,1H), 8.25 (s, 1H), 8.50 (s, 1H), 10.8 (s, 1H).

Example 9

N-(2-Amino-1,1-dimethylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl] oxalamide trifluoroacetate (1:1)

26 mg (0.29 mmol) of tert-butyl [2-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropyl]carbamate was dissolved and stirred in 10 ml of a 1:1 mixture of 1,1,1-trifluoroacetic acid and dichloromethane. After 1 hour the solvent mixture was co-evaporated with toluene three times and dichloromethane twice. The resulting gum was then triturated with 40-60 petroleum ether to give 124 mg of N-(2-amino-1,1-dimethylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate (1:1) as a yellow solid, ^{1}H NMR (400MHz, d6 DMSO) δ: 1.40 (s,6H), 3.20 (m,2H), 3.90 (s, 3H), 7.50 (s,1H), 7.60-7.74 (m, 2H), 7.80 (s, 1H), 7.90 (s(br), 3H), 8.30 (s,1H), 8.40 (s,1H), 10.80(s,1H).

The previously described trifluoroacetic acid salt was partitioned between a saturated sodium hydrogencarbonate solution and ethyl acetate. The organic layer was then dried with magnesium sulphate, filtered and evaporated to give the free base used in Example 10.

Example 10

N-(3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[2-(3,3-dimethylbutyramido)-1,1-dimethylethyl]oxalamide

30 mg (0.09 mmol) of N-(2-amino-1,1-dimethyl-ethyl)-N'-(3-methoxy-4-oxazol-5-yl-phenyl)-oxalamide, 52 mg (0.45 mmol) of tert-butylacetic acid, 86 mg (0.45 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 69 mg of HOAt were dissolved and stirred in 2 ml of dimethylformamide. After stirring for 16 hours the mixture was diluted with 10 ml of dichloromethane and washed with 10% citric acid solution in water, saturated sodium hydrogen carbonate solution and brine. The organic solution was then dried with solid magnesium sulphate, filtered and evaporated to give N-(3-methoxy-4-(5-oxazolyl)phenyl]-N'-[2-(3,3-dimethylbutyramido)-1,1-dimethylethyl]oxalamide as a pale yellow solid, MS: m/e 431.3 [M+H]+

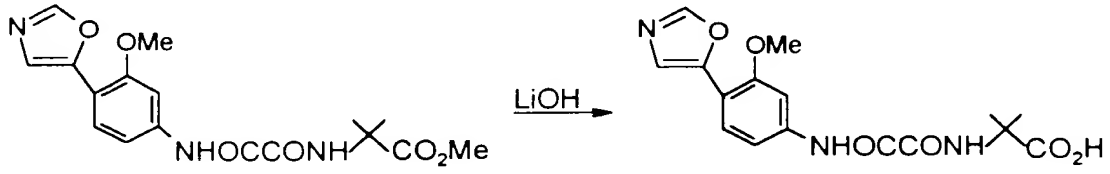
Example 11

N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[2-(4-methylbenzylamino)-1,1-dimethylethyl]oxalamide

30 mg (0.09 mmol) of N-(2-amino-1,1-dimethyl-ethyl)-N'-(3-methoxy-4-oxazol-5-yl-phenyl)-oxalamide, 11.3 mg (0.095 mmol) of 4-methylbenzaldehyde and 30 mg (0.14 mmol) of sodium triacetoxyborohydride were dissolved in 2ml of a 5% acetic acid dichloromethane mixture for 16 hours. The reaction mixture was then diluted with 8 ml of dichloromethane and washed with water, saturated sodium hydrogen carbonate and brine. The resulting organic solution was then dried with magnesium sulphate, filtered and evaporated to give N-[3-methoxy-4-(5-oxazolyl)phenyl]-N'-[2-(4-methylbenzylamino)-1,1-dimethylethyl]oxalamide as a yellow solid MS: m/e 437.3 [M+H]+.

Example 12

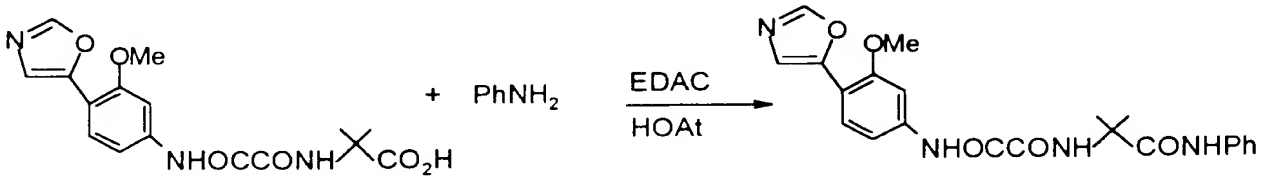
2-[[[3-Methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropionic acid



A mixture of 161 mg (0.446 mmol) of methyl 2-[[3-methoxy-4-(5-oxazolyl)anilinooxalyl]amino]-2-methylpropionate and 56 mg (1.33 mmol) of lithium hydroxide hydrate in 3 ml of methanol and 0.5 ml of water was heated at 50°C for 2 hours then diluted with water and washed with diethyl ether. The aqueous phase was acidified to pH2 with 2M hydrochloric acid and extracted twice with ethyl acetate. The combined organic extracts were dried over magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (120:15:3:2) for the elution. After trituration with ether there was obtained 70 mg of 2-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropionic acid as a white solid. MS: m/e 247.9 $[M+H]^+$.

Example 13

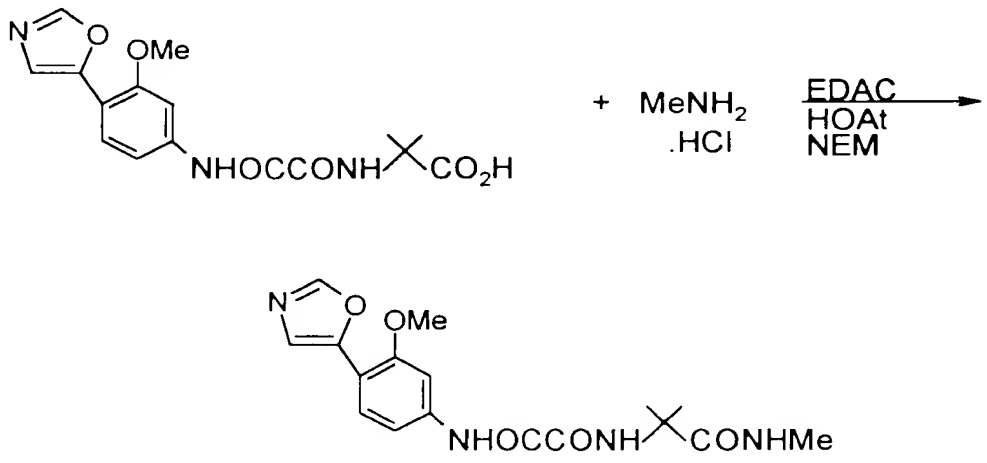
N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[1-methyl-1-(phenylcarbamoyl)ethyl]oxalamide



A solution of 30 mg (0.086 mmol) of 2-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropionic acid, 16 mg (0.172 mmol) of aniline, 18 mg (0.132 mmol) of 1-hydroxy-7-azabenzotriazole and 25 mg (0.131 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 2 ml of dimethylformamide was stirred at room temperature for 18 hours then diluted with ethyl acetate and washed with 2M hydrochloric acid and saturated sodium bicarbonate. The organic phase was dried over magnesium sulphate and after evaporation the residue was triturated with diethyl ether and collected by filtration to give 20 mg of N-[3-methoxy-4-(5-oxazolyl)phenyl]-N'-[1-methyl-1-(phenylcarbamoyl)ethyl]oxalamide as a white solid. MS: m/e 423.0 $[M+H]^+$.

Example 14

N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[1-methyl-1-(methylcarbamoyl)ethyl]oxalamide

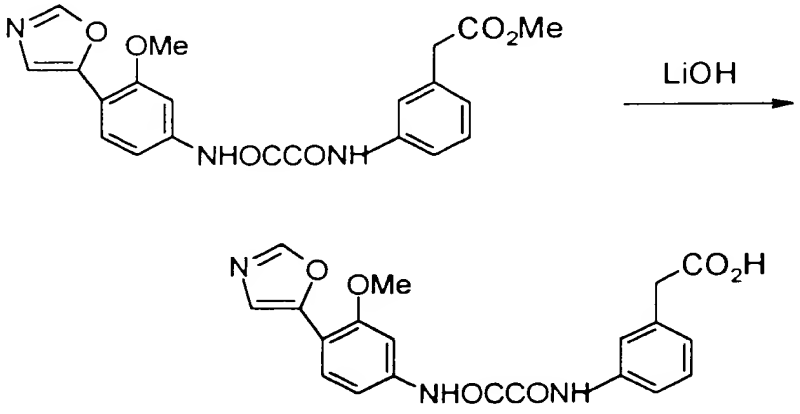


A mixture of 30 mg (0.086 mmol) of 2-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropionic acid, 12 mg (0.178 mmol) of methylamine hydrochloride, 18 mg (0.132 mmol) of 1-hydroxy-7-azabenzotriazole, 25 mg (0.131 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 22 mg (0.218 mmol) of triethylamine in 2 ml of dimethylformamide was stirred at room temperature for 18 hours then diluted with ethyl acetate and washed with 2M hydrochloric acid and saturated sodium bicarbonate. The organic solution was dried

over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using dichloromethane/methanol (24:1) for the elution. After trituration with ether there was obtained 17 mg of N-[3-methoxy-4-(5-oxazolyl)phenyl]-N'-[1-methyl-1-(methylcarbamoyl)ethyl]oxalamide as a white solid. MS: m/e 361.0 $[M+H]^+$.

Example 15

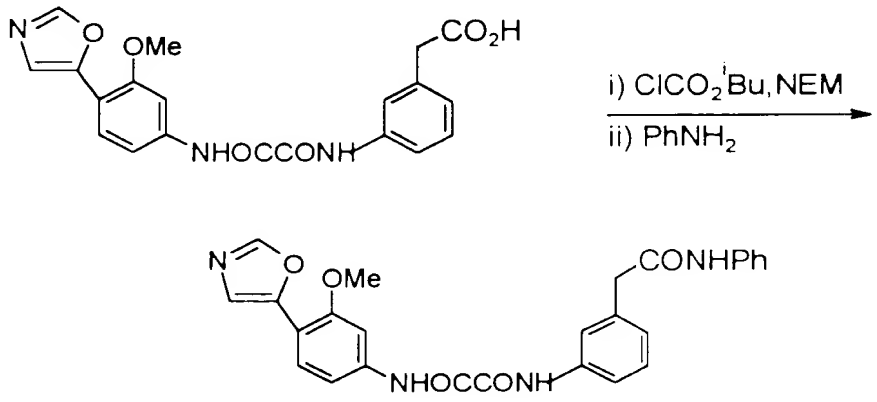
2-[3-[[[3-Methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]phenyl]acetic acid



A solution of 740 mg (1.81 mmol) of methyl 2-[3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]phenyl]acetate and 152 mg (3.62 mmol) of lithium hydroxide hydrate in 10 ml of methanol, 10 ml of 1,4-dioxane and 5 ml of water was stirred at room temperature for 18 hours. The solvent was removed by evaporation and the residue dissolved in water. The aqueous solution was washed with diethyl ether and acidified with citric acid solution. The solid which precipitated was collected by filtration and washed with water, ethanol and diethyl ether to give 414 mg of 2-[3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]phenyl]acetic acid as a white solid. MS: m/e 396.0 $[M+H]^+$.

Example 16

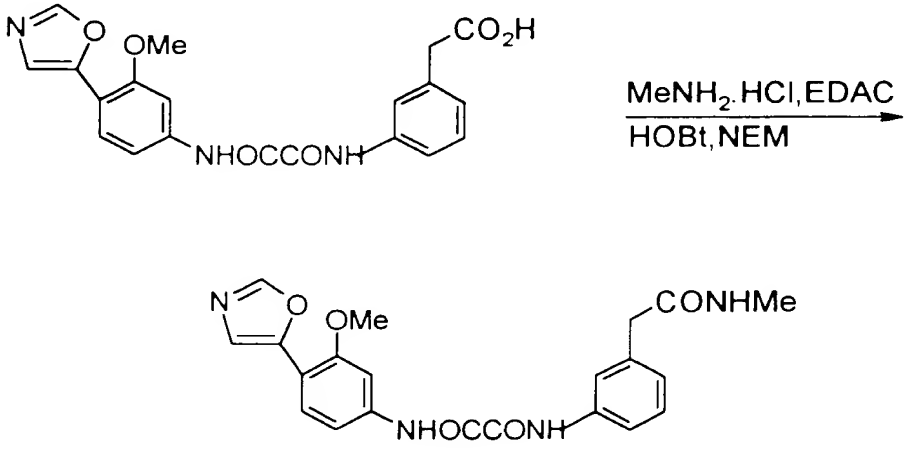
N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[3-[(phenylcarbamoyl)methyl] phenyl]oxalamide



A solution of 30 mg (0.076 mmol) of 2-[3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]phenyl]acetic acid and 11 mg (0.096 mmol) of N-ethylmorpholine in 1 ml of dimethylformamide was cooled to 0°C and a solution of 12 mg (0.088 mmol) of isobutyl chloroformate in 1 ml of dichloromethane was added. The resulting mixture was stirred for 30 minutes at 0°C then a solution of 7 mg (0.075 mmol) of aniline in 1 ml of dichloromethane was added and stirring was continued for a further hour at 0°C. After 18 hours at room temperature the mixture was evaporated to dryness and the residue chromatographed on silica gel using dichloromethane/methanol (19:1) for the elution. There was obtained 3 mg of N-[3-methoxy-4-(5-oxazolyl)phenyl]-N'-[3-[(phenylcarbamoyl)methyl]phenyl]oxalamide as a white solid MS: m/e 471.0 $[M+H]^+$.

Example 17

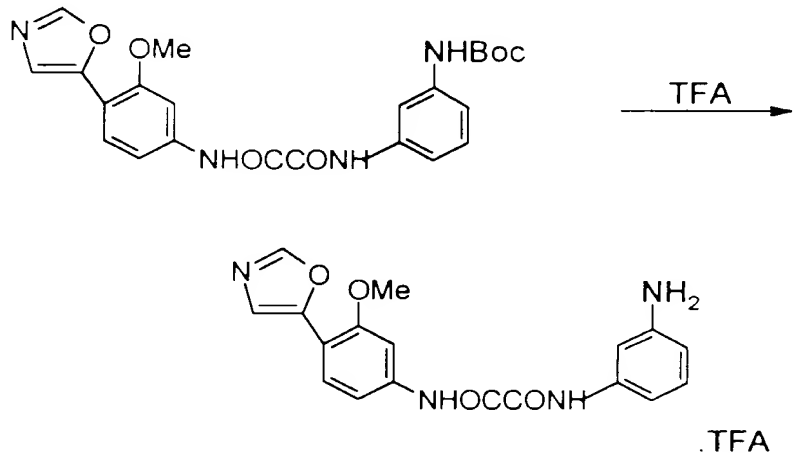
N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[3-[(methylcarbamoyl)methyl] phenyl]oxalamide



A mixture of 30 mg (0.076 mmol) of 2-[3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]phenyl]acetic acid, 22 mg (0.115 mmol) of 1-(3-dimethylaminopropyl)-3-ethylacrbodiimide hydrochloride, 14 mg (0.092 mmol) of 1-hydroxybenzotriazole hydrate, 26 mg (0.385 mmol) of methylamine hydrochloride and 52 mg (0.452 mmol) of N-ethylmorpholine in 1 ml of dimethylformamide was stirred at room temperature for 18 hours. The solvent was removed by evaporation and the residue chromatographed on silica gel using dichloromethane/methanol (1:19) for the elution. There was obtained 15 mg of N-[3-methoxy-4-(5-oxazolyl)phenyl]-N'-[3-[(methyl carbamoyl)methyl]phenyl]oxalamide as a white solid. MS: m/e 409 $[M+H]^+$.

Example 18

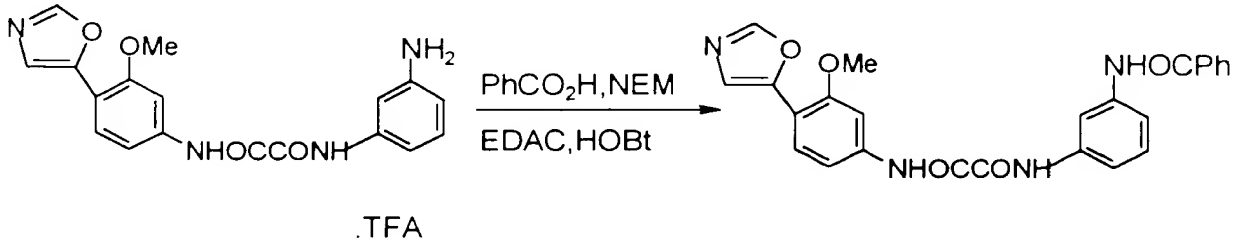
N-(3-Aminophenyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate



20 mg (0.043 mmol) of tert-butyl [3-[[[3-methoxy-4-(5-oxazolyl) anilino]oxalyl]amino]phenyl]carbamate were dissolved in a mixture of 1 ml of dichloromethane and 1 ml of trifluoroacetic acid at room temperature for 10 minutes. The solvent was removed by evaporation and the residue triturated with diethyl ether. The resulting solid was collected by filtration to give 18 mg of N-(3-aminophenyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate as a white solid. MS: m/e 394.0 $[M+H+MeCN]^+$.

Example 19

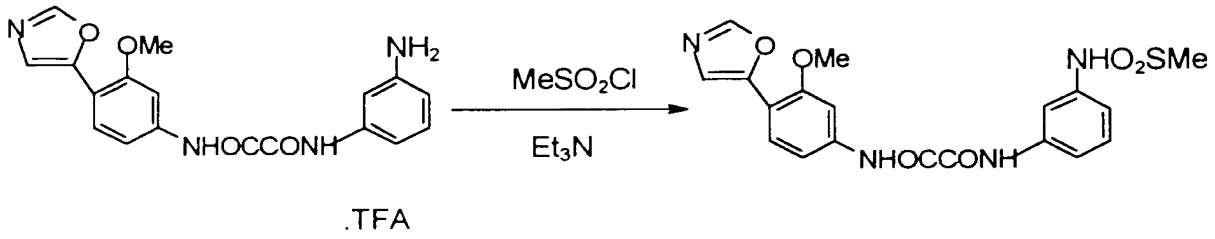
N-[3-(Benzamido)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide



A mixture of 30 mg (0.064 mmol) of N-(3-aminophenyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate, 9 mg (0.074 mmol) of benzoic acid, 15 mg (0.078 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 15 mg (0.096 mmol) of 1-hydroxybenzotriazole hydrate and 22 mg (0.19 mmol) of N-ethylmorpholine in 0.5 ml of dimethylformamide was stirred at room temperature for 18 hours then diluted with ethyl acetate and washed with 10% citric acid solution, saturated sodium bicarbonate and water. The organic phase was dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using dichloromethane/methanol (19:1) for the elution. There was obtained after trituration with diethyl ether/petrol (1:1). 12 mg of N-[3-(benzamidophenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide as a white solid. MS: m/e 457.0 $[M+H]^+$.

Example 20

N-[3-(Methanesulphonamido)phenyl]-N'-[3-methoxy-4-(5-oxazolyl) phenyl]oxalamide

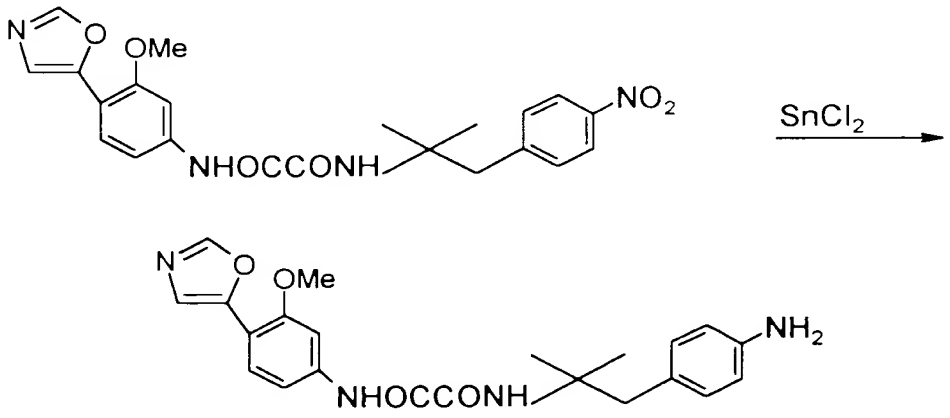


12 mg (0.011 mmol) of methanesulphonyl chloride were added to a solution of 50 mg (0.011 mmol) of N-(3-aminophenyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate and 32 mg (0.317 mmol) of triethylamine in 0.5 ml of dimethylformamide. The resulting solution was left at room temperature for 18 hours then diluted with ethyl acetate and washed with 10% citric acid solution, saturated sodium bicarbonate and water. The organic phase was dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using

ethyl acetate/petrol (1:1) for the elution. There was obtained 5 mg of N-[3-(methanesulphonamido)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide as a white solid. MS: m/e 431.0 $[M+H]^+$.

Example 21

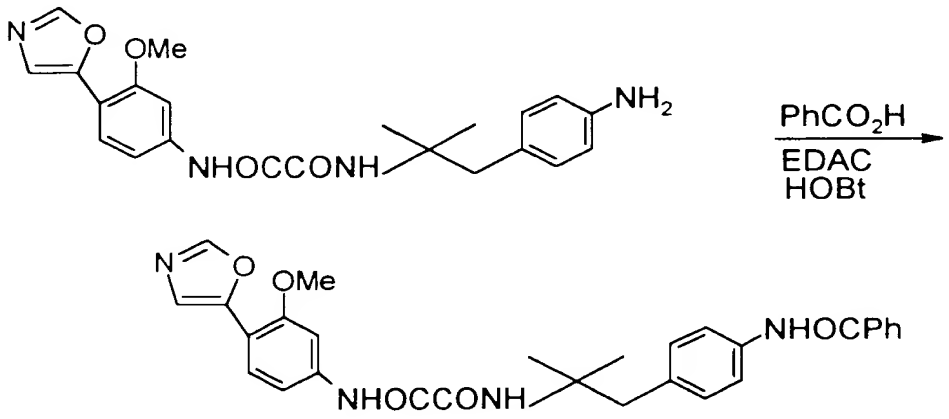
N-[2-(4-Aminophenyl)-1,1-dimethylethyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide



A mixture of 44 mg (0.1 mmol) of N-[3-methoxy-4-(5-oxazolyl)phenyl]-N'-[1,1-dimethyl-2-(4-nitrophenyl)ethyl]oxalamide and 90 mg (0.5 mmol) of tin(II) chloride were stirred and heated at 85°C in 2 ml of ethanol and 1 ml of 1,4-dioxane for 5 hours. The resulting solution was cooled, diluted with ethyl acetate and washed with 2M sodium hydroxide. The organic phase was dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate/petrol (2:1) for the elution. After trituration with petrol there was obtained 31mg of N-[2-(4-aminophenyl)-1,1-dimethylethyl]-N'-[3-methoxy-4-(5-oxazolyl) phenyl]oxalamide as a white solid. MS: m/e 409 $[M+H]^+$.

Example 22

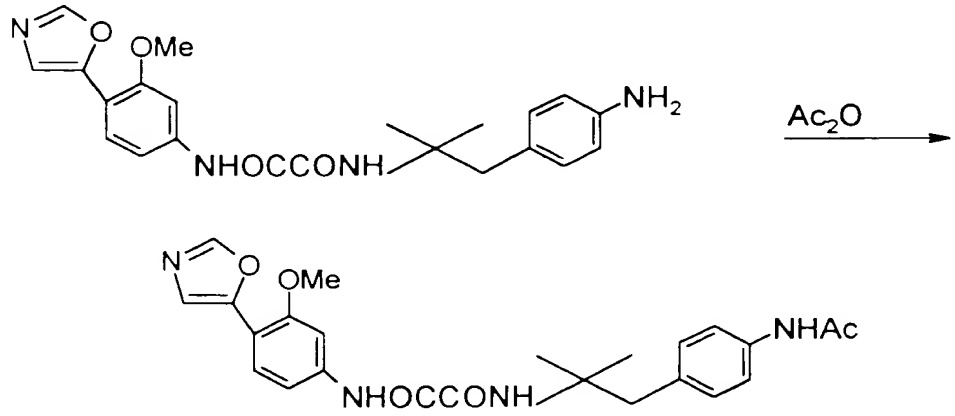
N-[2-(4-Benzamidophenyl)-1,1-dimethylethyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl] oxalamide



A mixture of 30 mg (0.074 mmol) of N-[2-(4-aminophenyl)-1,1-dimethylethyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide, 10 mg (0.082 mmol) of benzoic acid, 14 mg (0.092 mmol) of 1-hydroxybenzotriazole hydrate, 21 mg (0.11 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 18 mg (0.16 mmol) of N-ethylmorpholine in 2 ml of dichloromethane was stirred at room temperature for 18 hours then diluted with dichloromethane and washed with 2M hydrochloric acid and saturated sodium bicarbonate. The organic phase was dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate/petrol (2:1) for the elution. There was obtained 9 mg of N-[2-(4-benzamidophenyl)-1,1-dimethylethyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide as a white solid. MS: m/e 513 $[M+H]^+$.

Example 23

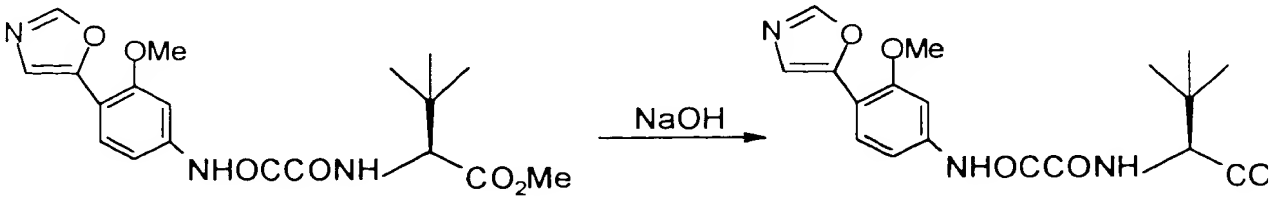
N-[2-(4-Acetamidophenyl)-1,1-dimethylethyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl] oxalamide



A mixture of 30 mg (0.074 mmol) of N-[2-(4-aminophenyl)-1,1-dimethylethyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide, 8 mg (0.078 mmol) of acetic anhydride and 17 mg (0.15 mmol) of N-ethylmorpholine in 1 ml of dichloromethane was stirred at room temperature for 2 hours. The solvent was removed by evaporation and the residue triturated with diethyl ether and collected by filtration to give 14 mg of N-[2-(4-acetamidophenyl)-1,1-dimethylethyl]-N'-[3-methoxy-4-(5-oxazolyl) phenyl]oxalamide as a white solid. MS: m/e 451 $[M+H]^+$.

Example 24

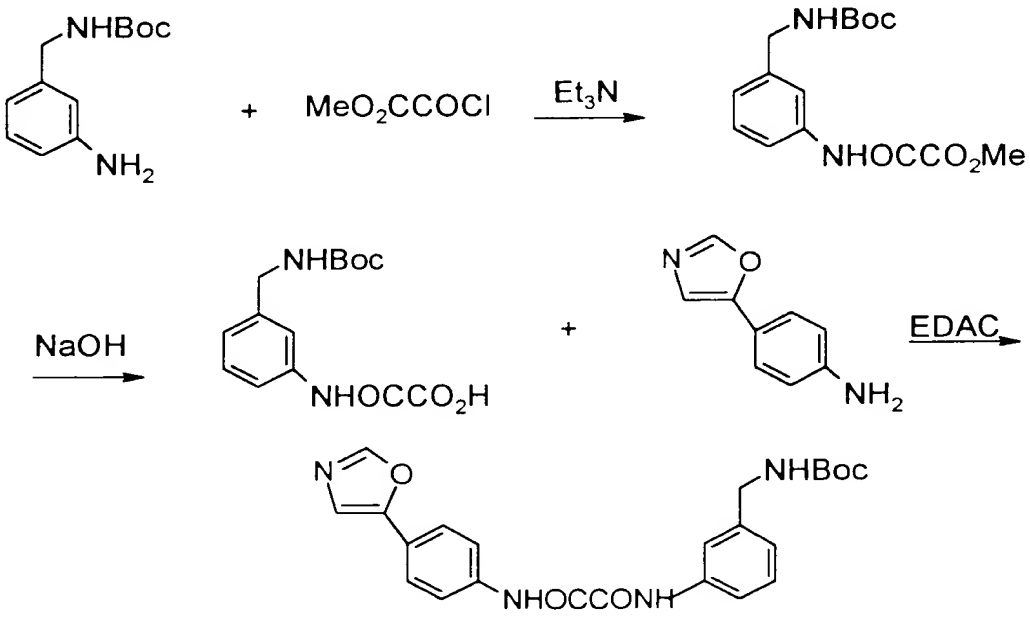
N2-[[3-Methoxy-4-(5-oxazolyl)anilino]oxalyl]-N1,3-dimethyl-L-valinamide



290 mg (0.75 mmol) of N-[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]-3-methyl-L-valine methyl ester in 3 ml of methanol and 1 ml of 1M aqueous sodium hydroxide were warmed gently and the resulting solution left at room temperature for 18 hours. The mixture was diluted with water, washed with diethyl ether and the aqueous phase acidified with 2M hydrochloric acid. The solution was extracted with ethyl acetate and the organic phase dried over magnesium sulphate, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate/acetic acid (99:1) for the elution. After trituration with diethyl ether there was obtained 110 mg of N2-[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]-N1,3-dimethyl-L-valinamide as a white solid. MS: m/e 376.0 $[M+H]^+$.

Example 25

Tert-butyl [3-[[[4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate



In an analogous manner to that described in Example 1 but replacing 3-methoxy-4-(5-oxazolyl)aniline with 4-(5-oxazolyl)aniline and N-tert-butyloxalamic acid with N-[3-[(tert-butoxyformamido)methyl]phenyl]oxamic acid there was obtained tert-butyl [3-[[[4-(5-oxazolyl)anilino] oxalyl]amino]benzyl]carbamate as a white solid. ^{1}H NMR (400 MHz, DMSO) δ: 1.4 (9H,s), 4.1 (2H,d), 7.02 (1H,d), 7.32 (1H,t), 7.40 (1H,t), 7.63 (1H,s), 7.69 (1H,d), 7.70-7.79 (3H,m, 7.97 (2H,d), 8.43 (1H,s), 10.82 (1H,s), 10.99 (1H,s).

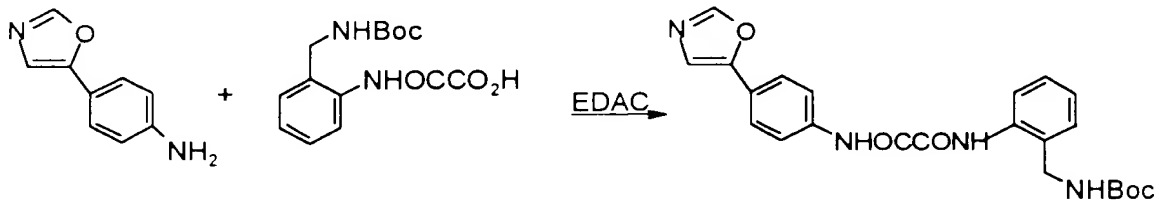
The starting material was prepared as follows:

i) 586 mg (4.78 mmol) of methyl oxalyl chloride were added to a solution of 1 g (4.5 mmol) of tert-butyl (3-aminobenzyl)carbamate and 508 mg (5.03 mmol) of triethylamine in 10 ml of dichloromethane. The resulting solution was stirred at room temperature for 30 minutes then washed with 5% citric acid solution and saturated sodium bicarbonate. The organic phase was dried over magnesium sulphate and the solvent removed by evaporation to give 1.5 g of methyl N-[3-[(tert-butoxyformamido)methyl]phenyl]oxamate as a viscous gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (9H,s), 3.96 (3H,s), 4.31 (2H,d) 4.9-5.0 (br.s, 1H), 7.11 (1H,d), 7.33 (1H,t), 7.51 (1H,s), 7.52 (1H,d), 8.86 (br.s. 1H).

ii) A mixture of 1.232 g (4 mmol) of methyl N-[3-[(tert-butoxy formamido)methyl] phenyl]oxamate and 0.24 g (6 mmol) of sodium hydroxide in 15 ml of methanol/water (2:1) was stirred at room temperature for 2 hours. The solvent was removed by evaporation and the residue dissolved in water and diethyl ether. The aqueous layer was acidified with citric acid and washed twice with ethyl acetate. The combined organic solutions were dried over magnesium sulphate and the solvent removed by evaporation to give 670 mg of N-[3-[(tert-butoxyformamido)methyl] phenyl]oxamic acid as a white solid. ^{1}H NMR (400 MHz, DMSO) δ: 1.48 (9H,s), 4.17 (2H,d), 7.09 (1H,d), 7.36 (1H,t), 7.49 (1H, t), 7.64 (1H,d), 7.74 (1H,s), 10.75 (1H,s).

Example 26

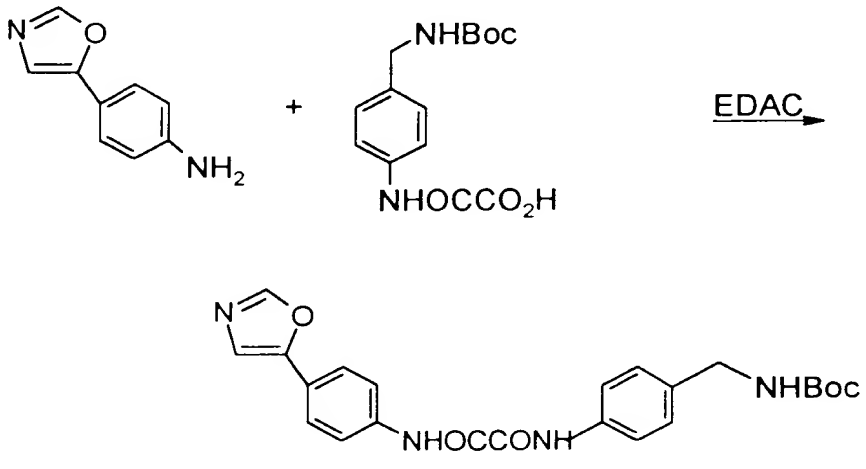
Tert-butyl [2-[[[4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate



In an analogous manner to that described in Example 25 but replacing N-[3-[(tert-butoxyformamido)methyl]phenyl]oxamic acid with N-[2-[tert-butoxyformamido)methyl]phenyl]oxamic acid there was obtained tert-butyl [2-[[[4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate as a white solid MS: m/e 437.0 $[M+H]^+$.

Example 27

Tert-butyl [4-[[[4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate

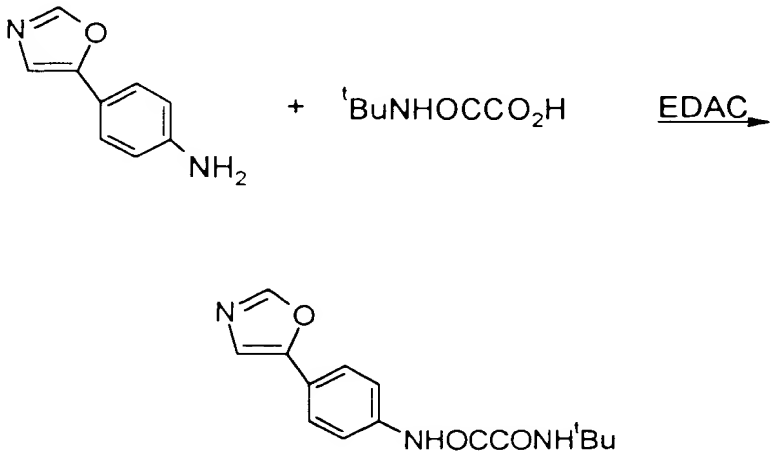


In an analogous manner to that described in Example 25 but replacing N-[3-[(tert-butoxyformamido)methyl]phenyl]oxamic acid with N-[4-[tert-butoxyformamido)

methyl]phenyl]oxamic acid there was obtained tert-butyl [4-[[[4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate as a white solid. MS: m/e 436.6 $[M]^+$.

Example 28

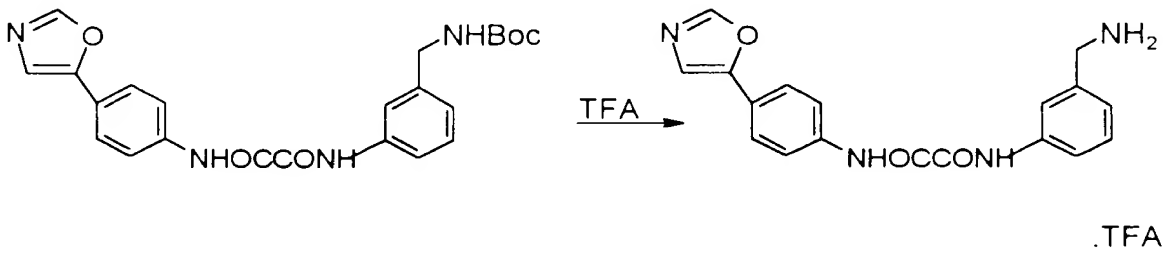
N-Tert-butyl-N'-[4-(5-oxazolyl)phenyl]oxalamide



In an analogous manner to that described in Example 1 but replacing 3-methoxy-4-(5-oxazolyl)aniline with 4-(5-oxazolyl)aniline there was obtained N-tert-butyl-N'-[4-(5-oxazolyl)phenyl]oxalamide as a pale yellow solid. MS: m/e 329.0 $[M+H+MeCN]^+$.

Example 29

N-[3-(Aminomethylphenyl]-N'-[4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate

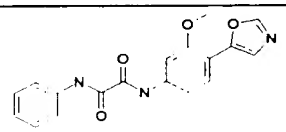
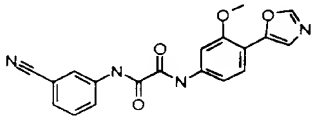
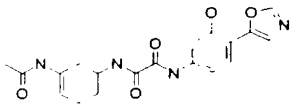
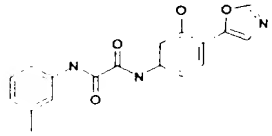
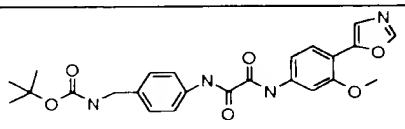


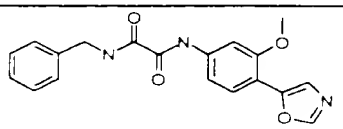
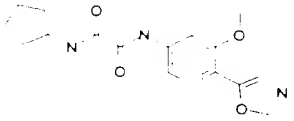
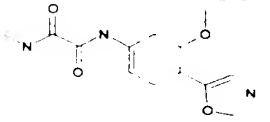
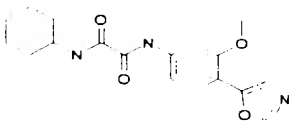
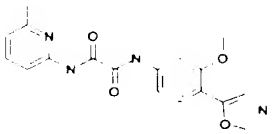
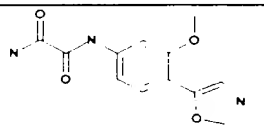
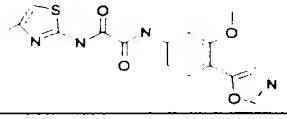
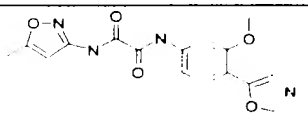
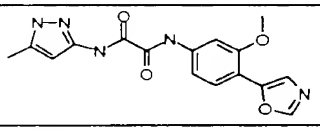
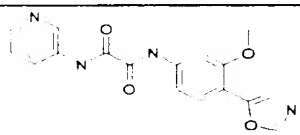
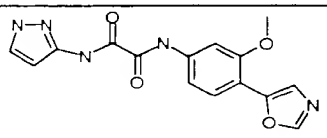
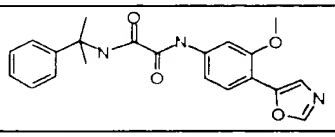
In an analogous manner to that described in Example 3 but replacing tert-butyl [3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carbamate with tert-butyl [3-[[[4-(5-oxazolyl)oxalyl]amino]benzyl]carbamate there was obtained N-[3-(aminomethylphenyl]-N'-[4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate as a white solid. MS: m/e 336 $[M]^+$.

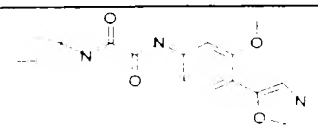
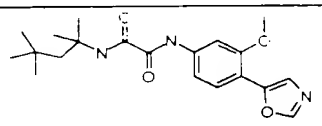
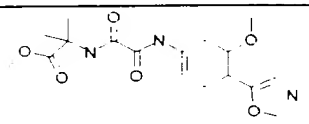
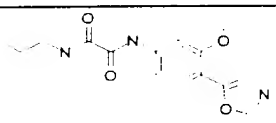
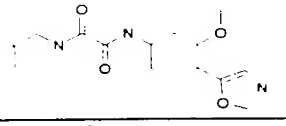
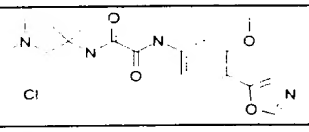
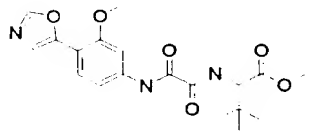
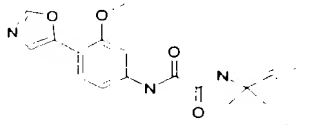
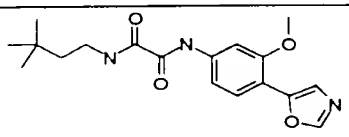
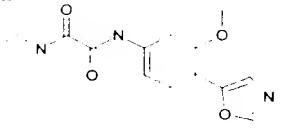
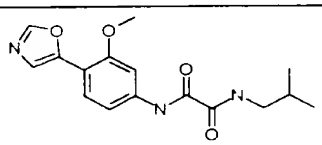
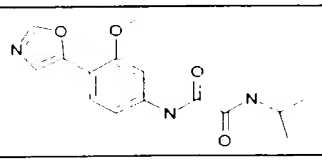
Examples 30-196

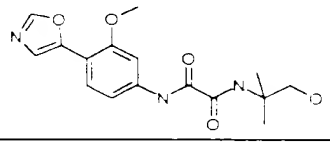
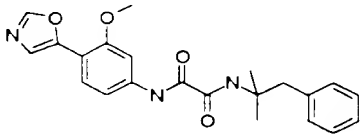
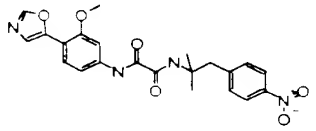
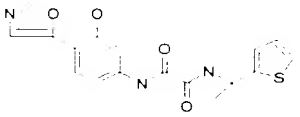
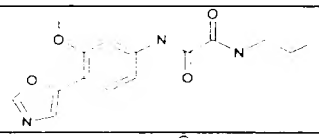
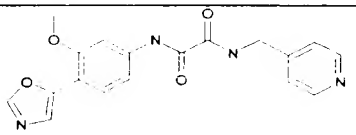
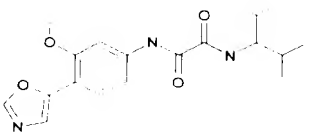
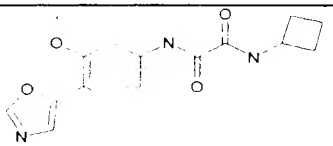
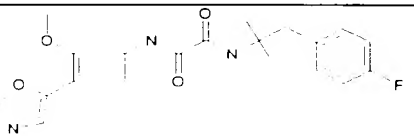
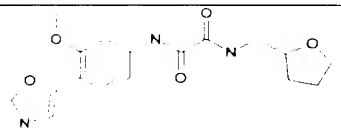
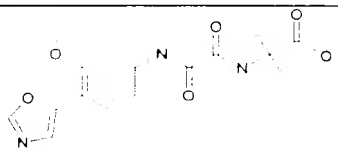
In a manner analogous to that described in Example 1, starting with N-[3-methoxy-4-(5-oxazoyl)phenyl oxalamic acid (prepared as described in Example 1, parts (i) and (ii)) and the appropriate amine the compounds shown in Table 3 were also prepared:

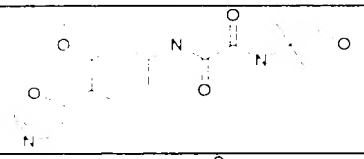
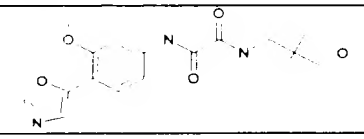
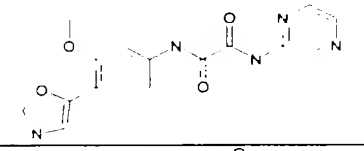
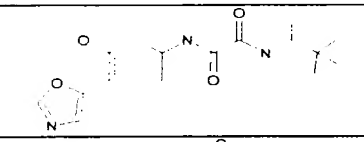
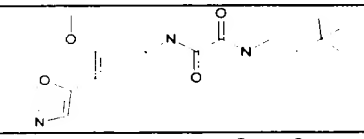
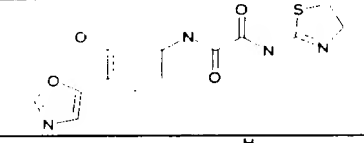
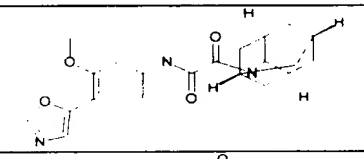
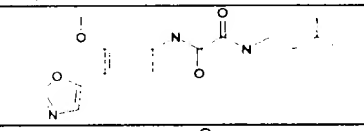
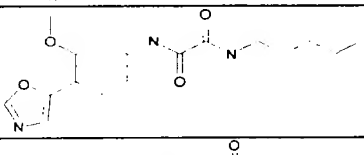
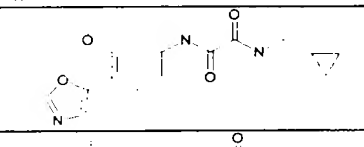
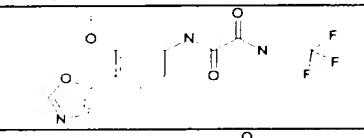
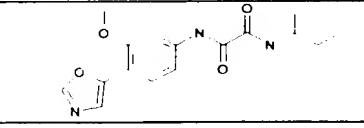
Table 3

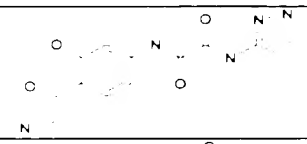
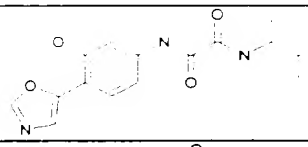
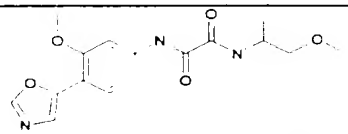
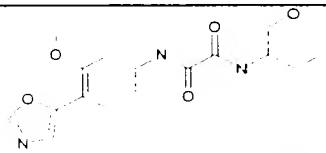
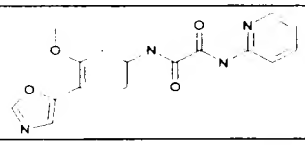
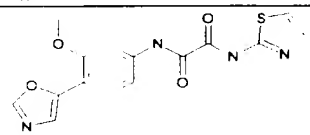
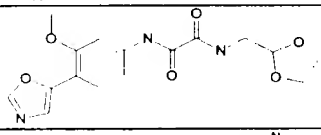
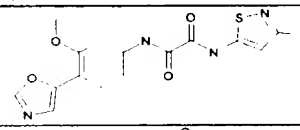
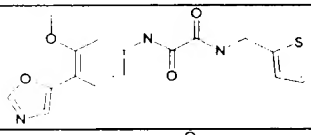
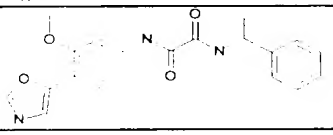
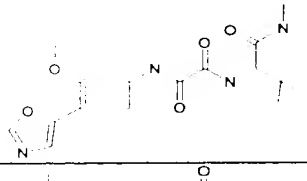
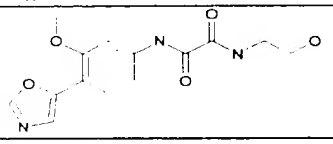
Example	Structure	MS(ES)
30.		338.0
31.		362.9
32.		395.0
33.		352.0
34.		466 (M^+;EI)

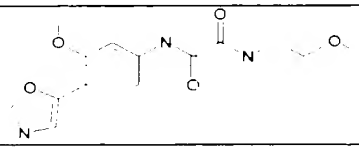
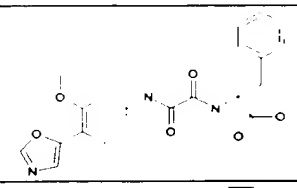
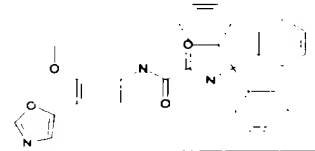
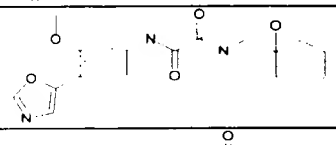
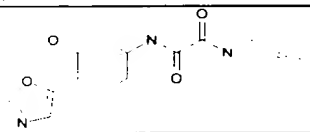
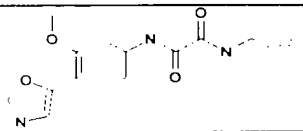
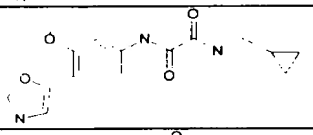
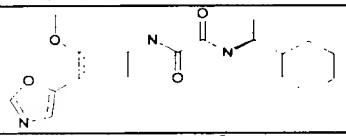
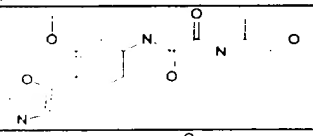
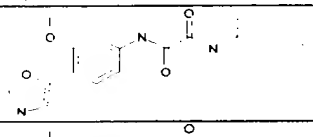
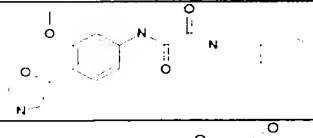
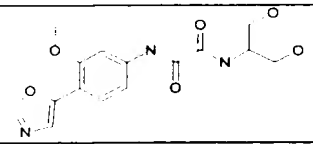
35.		352.0
36.		330.0
37.		275.9
38.		344.0
39.		352.9
40.		261.9
41.		358.9
42.		342.9
43.		341.9
44.		338.9
45.		327.9
46.		380.0

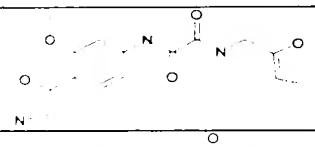
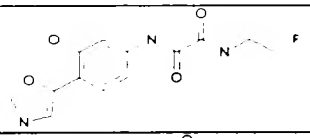
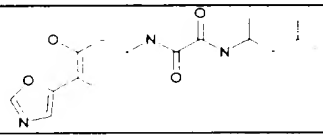
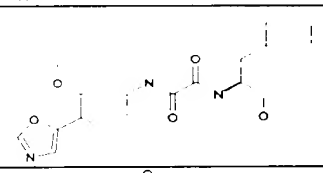
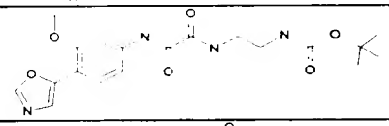
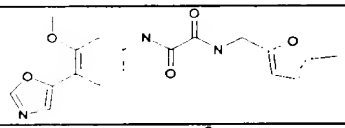
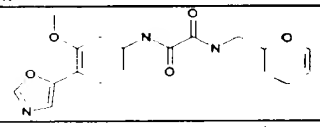
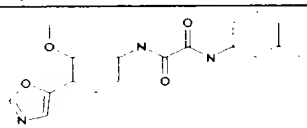
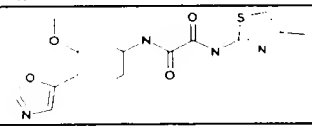
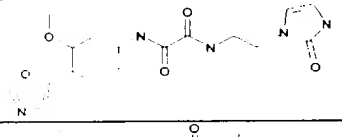
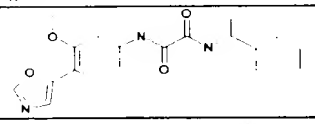
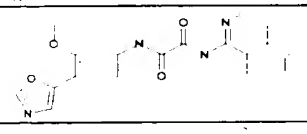
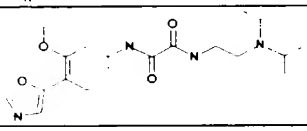
47.		332.0
48.		374.0
49.		362.0
50.		317.9
51.		332.0
52.		361.0
53.		389.9
54.		328.0
55.		346.0
56.		289.9
57.		318.0
58.		304.0

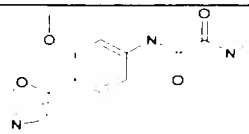
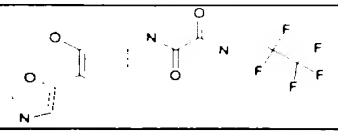
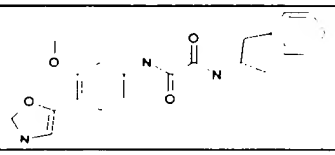
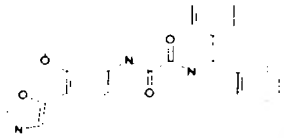
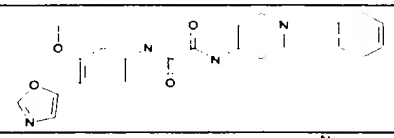
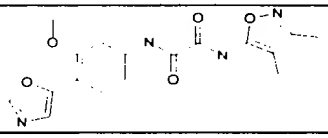
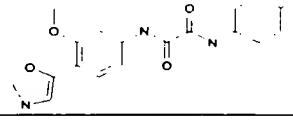
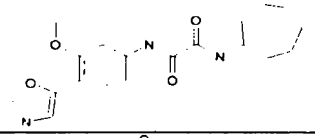
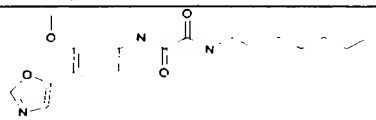
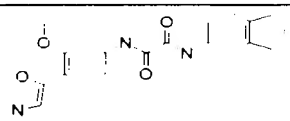
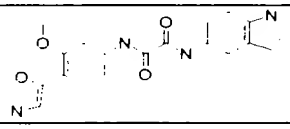
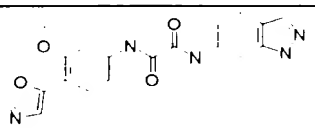
59.		333.9
60.		394.0
61.		439 (M^+;EI)
62.		386 (M^+;EI)
63.		304.0
64.		353.2
65.		360.2
66.		316.2
67.		412.2
68.		345.8
69.		362.4

70.		334.2
71.		348.0
72.		340.0
73.		345.8
74.		346.0
75.		346.8
76.		395.8
77.		332.4
78.		332.4
79.		316.2
80.		344.0
81.		317.8

82.		328.2
83.		332.4
84.		334.2
85.		334.2
86.		339.2
87.		344.8
88.		348.0
89.		359.2
90.		358.2
91.		366.2
92.		389.4
93.		306.2

94.		319.8
95.		438.0
96.		504.2
97.		374.0
98.		299.8
99.		302.2
100.		316.2
101.		372.0
102.		319.8
103.		332.4
104.		332.4
105.		336.6

106.		342.0
107.		308.0
108.		345.8
109.		402.0
110.		405.2
111.		356.0
112.		358.2
113.		358.2
114.		359.2
115.		374.0
116.		372.0
117.		389.2
118.		389.4

119.		276.0
120.		394 (M^+;EI)
121.		378.4
122.		428 (M^+;EI)
123.		435.2
124.		357.2
125.		358.2
126.		358.2
127.		360.2
128.		378.4
129.		377.4
130.		378.4

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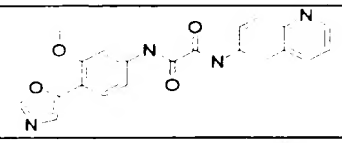
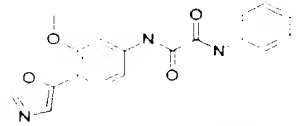
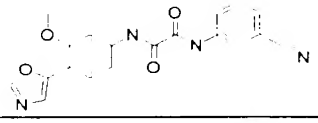
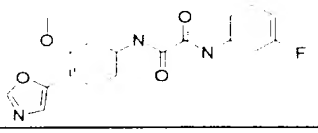
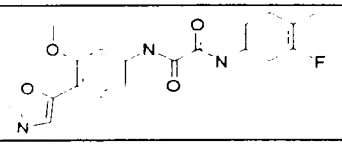
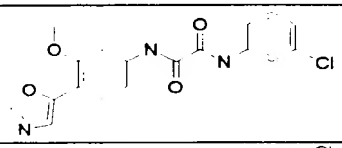
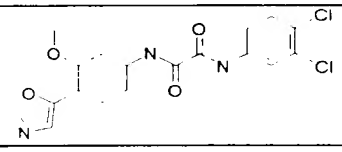
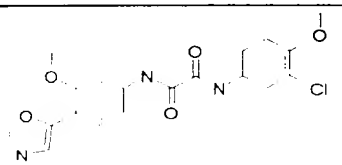
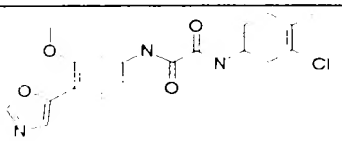
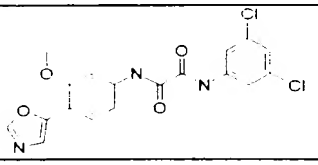
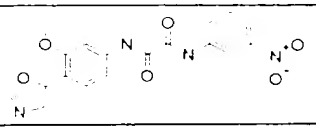
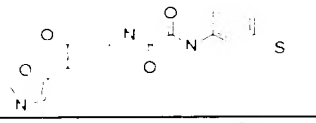
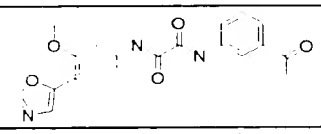
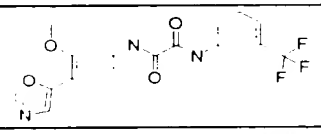
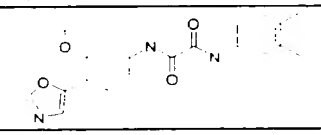
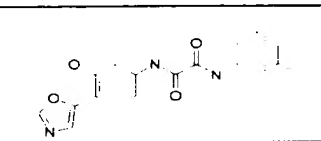
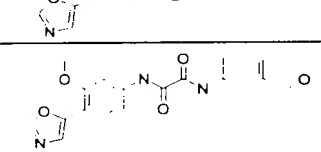
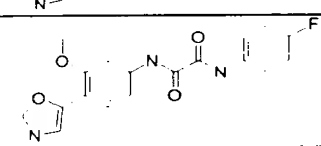
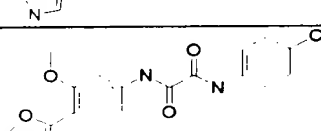
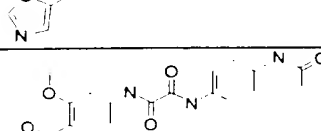
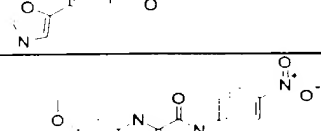
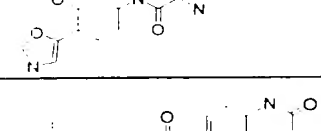
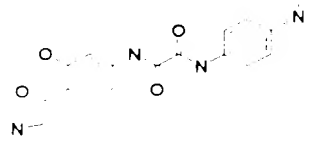
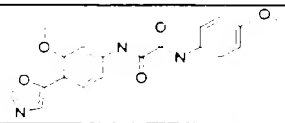
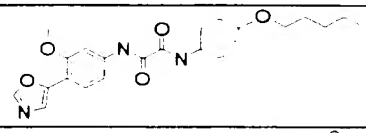
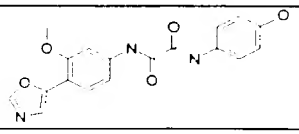
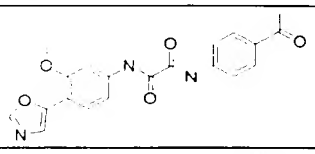
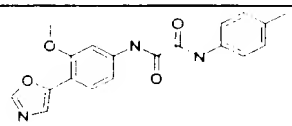
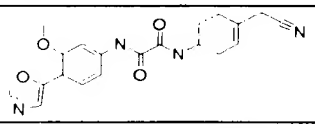
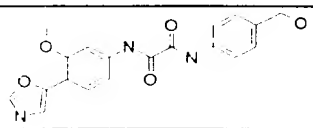
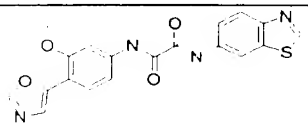
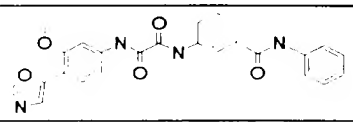
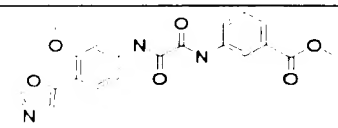
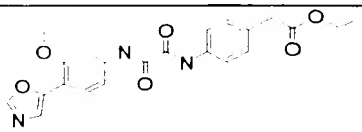
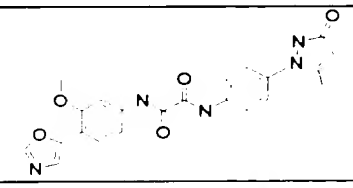
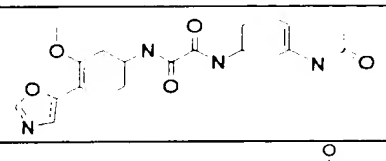
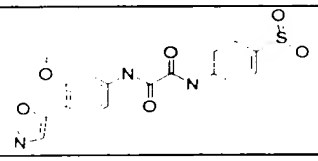
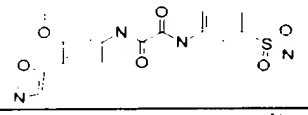
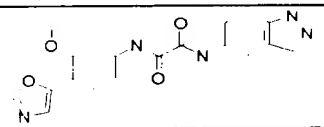
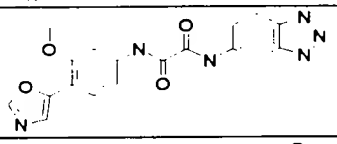
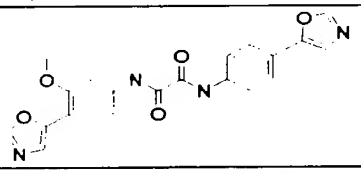
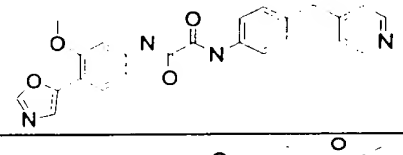
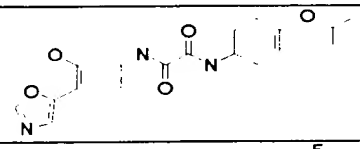
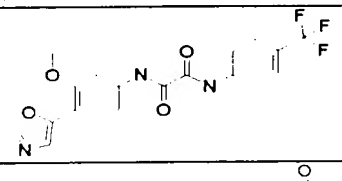
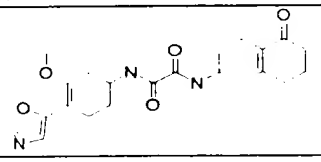
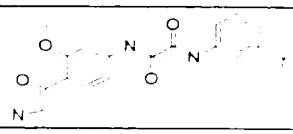
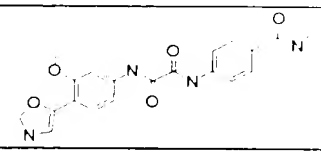
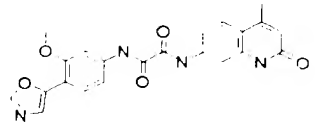
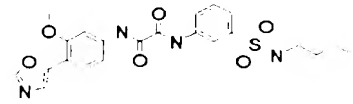
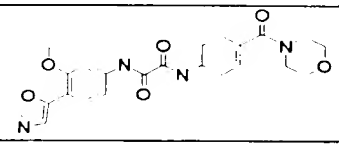
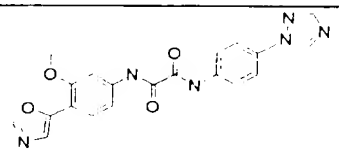
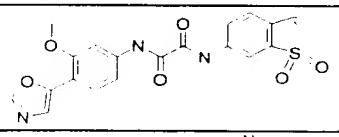
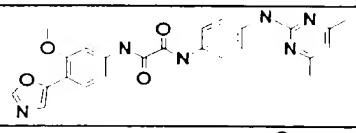
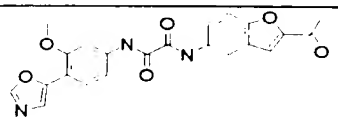
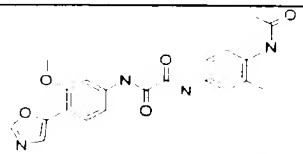
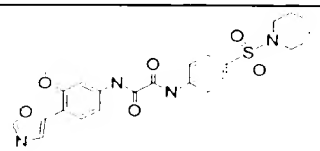
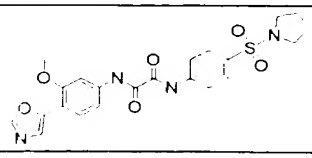
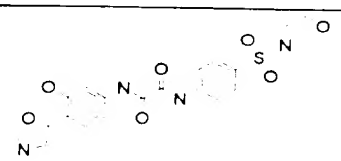
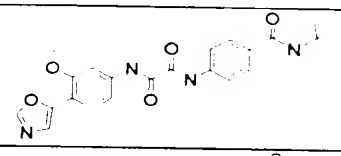
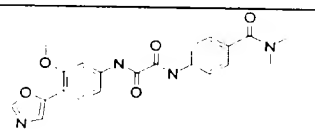
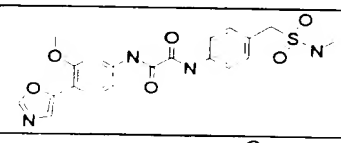
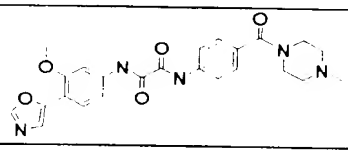
132.		389.4
133.		338.2
134.		363.4
135.		356
136.		370
137.		371.8
138.		406.2
139.		402.2
140.		386.2
141.		406.2

142.		383.2
143.		384
144.		380.2
145.		406.2
146.		366.2
147.		366.2
148.		368.2
149.		356
150.		371.8
151.		395
152.		383.2
153.		409.4

154.		380.8
155.		368.2
156.		424.2
157.		354.2
158.		380.2
159.		352.4
160.		377.4
161.		368.2
162.		395
163.		457.4
164.		396
165.		424

166.		434.2
167.		395
168.		416.4
169.		417.4
170.		378.4
171.		379.2
172.		405.2
173.		428.8
174.		396
175.		406.2
176.		406.2

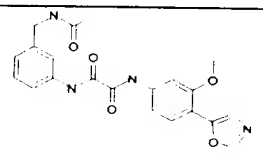
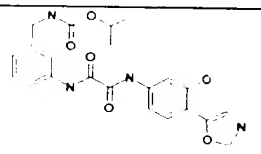
177.		394.2
178.		407
179.		507.2
180.		473.2
181.		451.2
182.		405.2
183.		426
184.		459.2
185.		420.2
186.		409.4
187.		485.4
188.		471.6

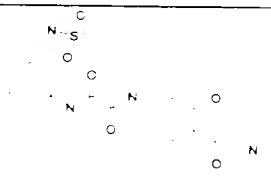
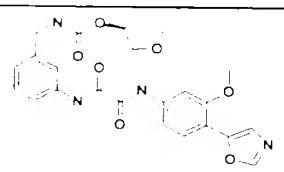
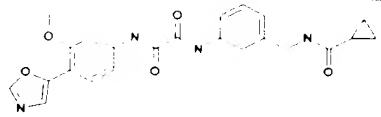
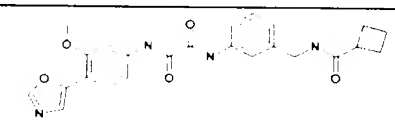
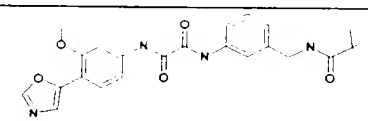
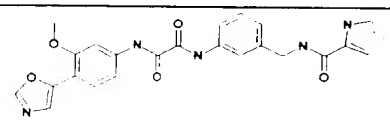
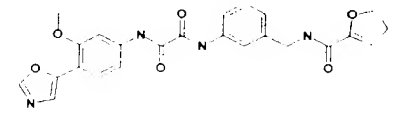
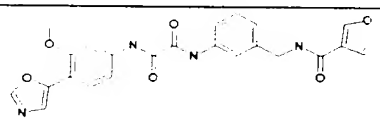
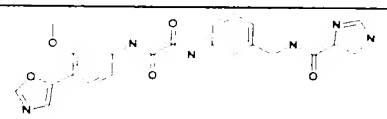
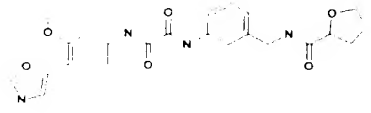
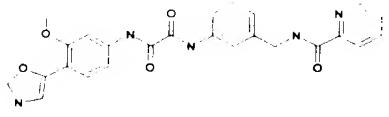
189.		487.2
190.		437.2
191.		409.4
192.		445.2
193.		464

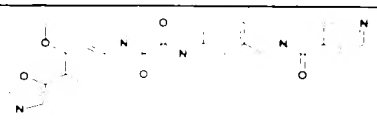
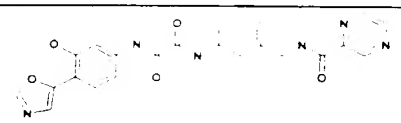
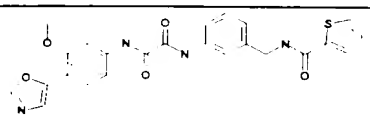
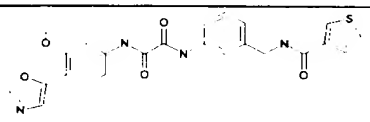
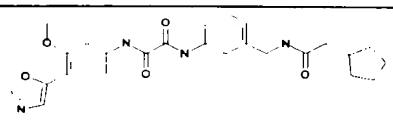
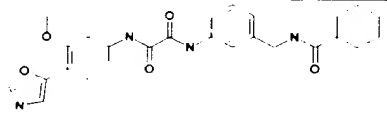
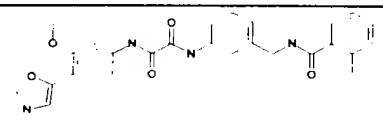
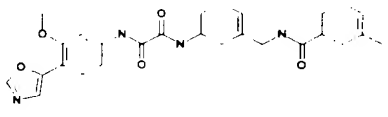
Examples 194- 214

In a manner analogous to that described in Example 4, starting with N-[3-(aminomethyl)phenyl]-N'-[3-methoxy-4-(5-(oxazolyl)phenyl]oxalamide trifluoroacetate (prepared as descibed in Example 3) and the appropriate carboxylic acid derivative the compounds shown in Table 5 also were prepared:

Table 5

Example	Structure	MS(ES)
194.		409.1
195.		453.0

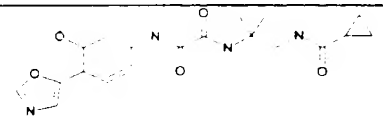
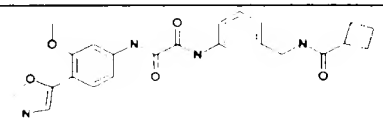
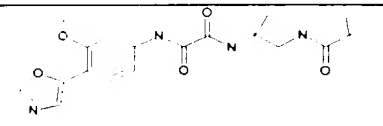
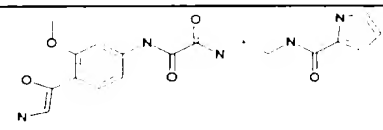
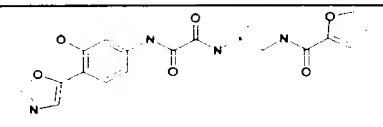
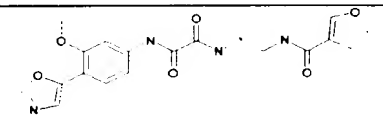
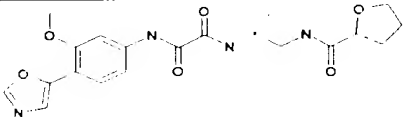
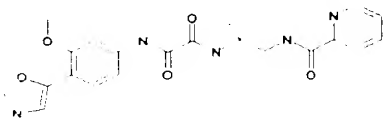
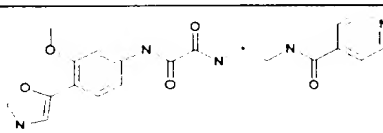
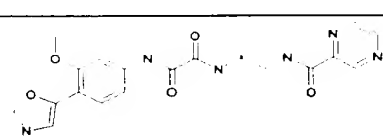
196.		445.0
197.		481.0
198.		435.1
199.		449.1
200.		451.2
201.		460.0
202.		461.1
203.		461.0
204.		461.0
205.		465.1
206.		472.1

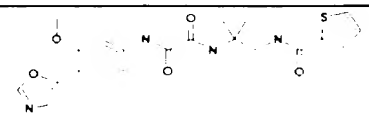
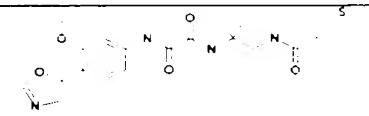
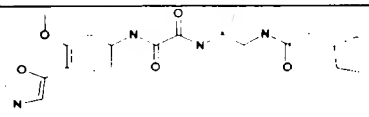
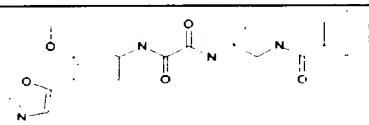
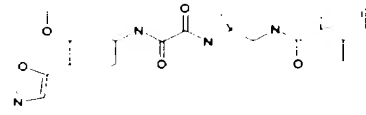
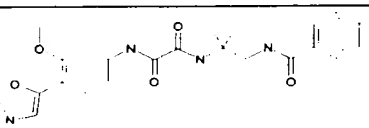
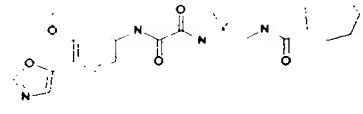
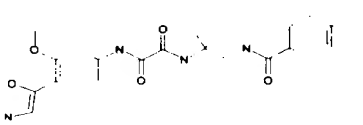
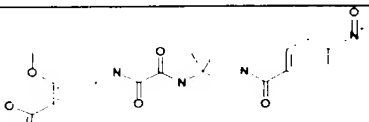
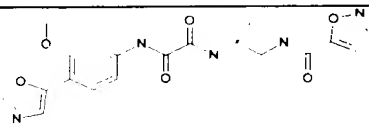
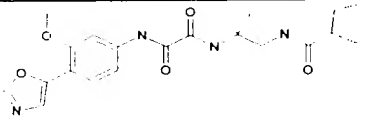
207.		472.0
208.		473.0
209.		477.0
210.		477.0
211.		477.2
212.		477.2
213.		485.1
214.		485.2

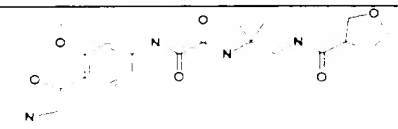
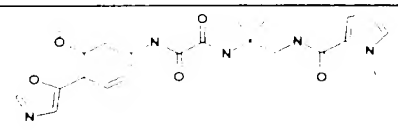
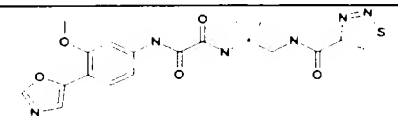
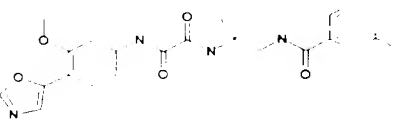
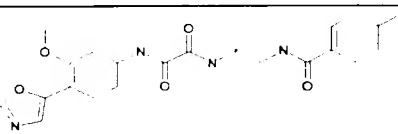
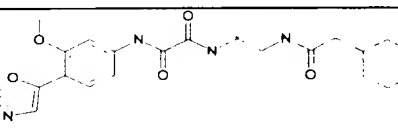
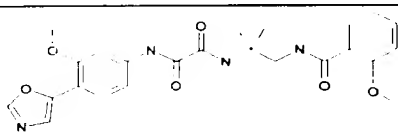
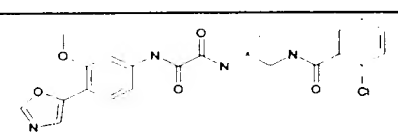
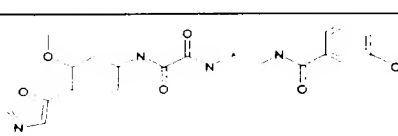
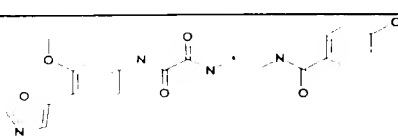
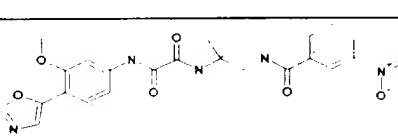
Examples 215 - 301

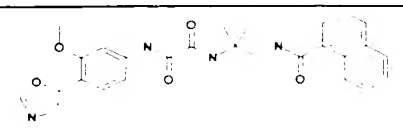
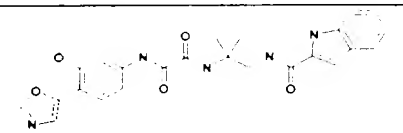
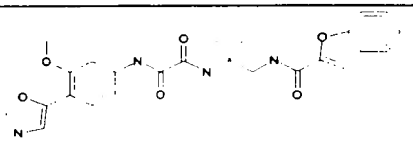
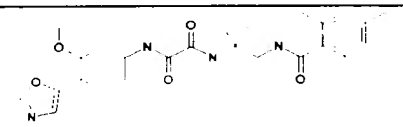
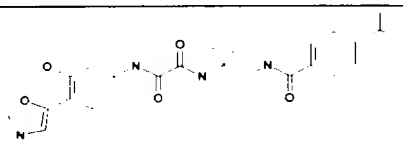
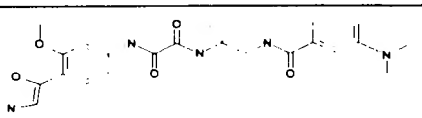
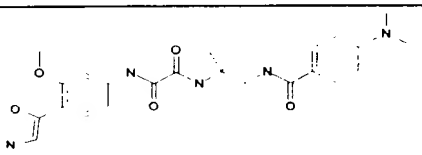
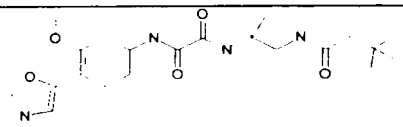
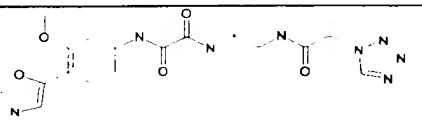
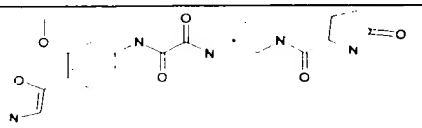
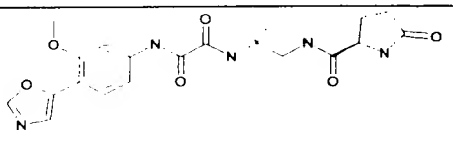
In a manner analogous to that described in Example 10, starting with N-[2-amino-1,1-dimethylethyl)-N'-(3-methoxy-4-oxazol-5-ylphenyl)oxalamide (prepared as described in Example 9) and the appropriate carboxylic acid the compounds shown in table 4 were also prepared:

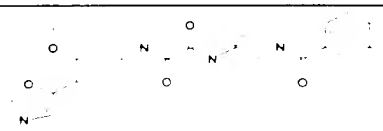
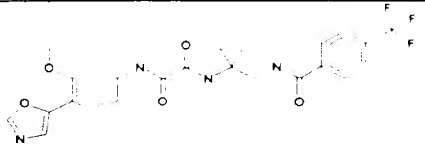
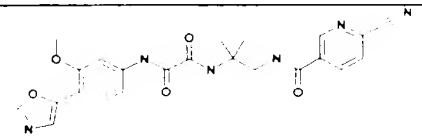
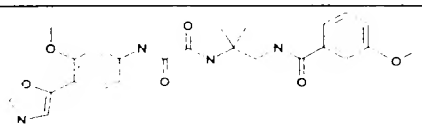
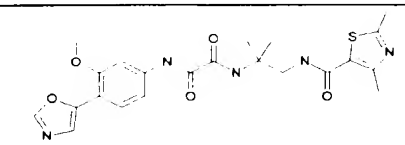
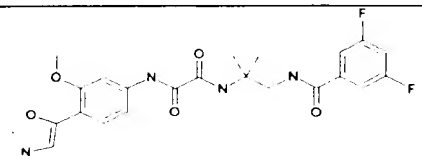
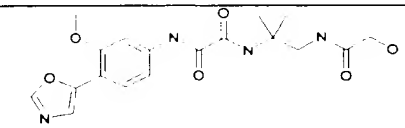
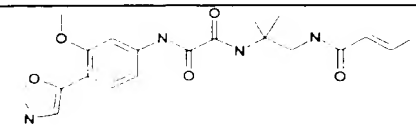
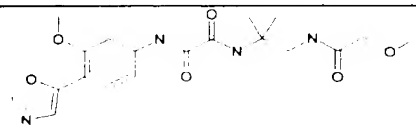
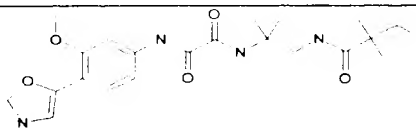
Table 4

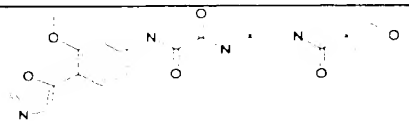
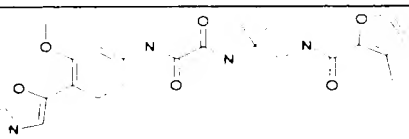
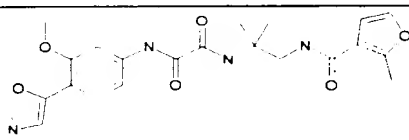
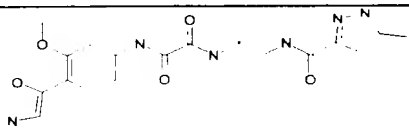
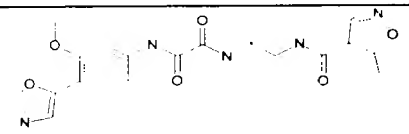
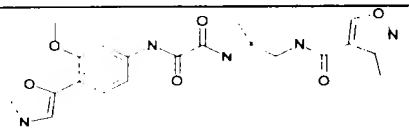
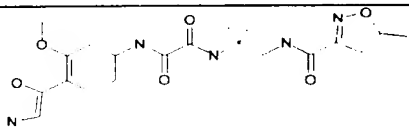
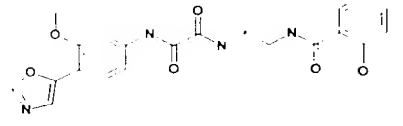
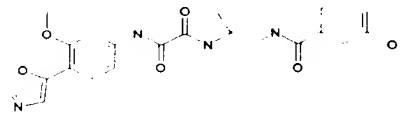
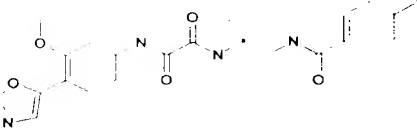
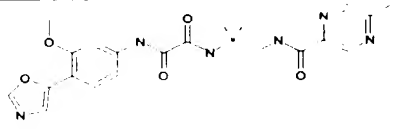
Example	Structure	MS(ES)
215.		401.0
216.		415.0
217.		417.0
218.		426.0
219.		427.0
220.		427.0
221.		431.0
222.		438.0
223.		438.0
224.		439.0

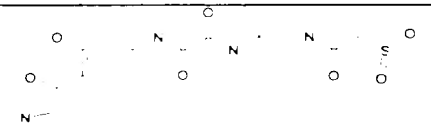
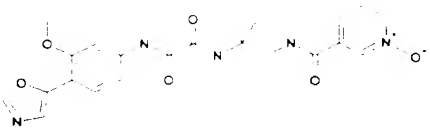
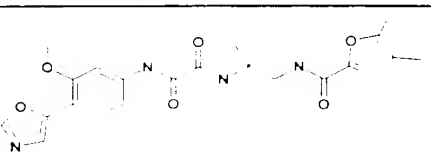
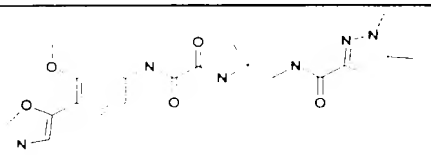
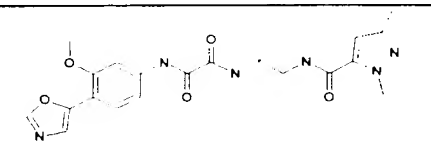
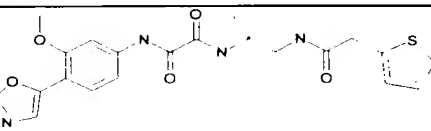
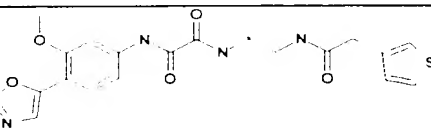
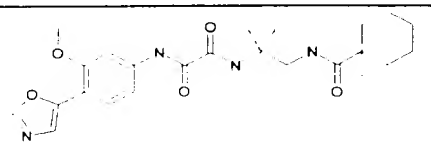
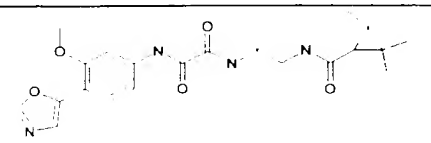
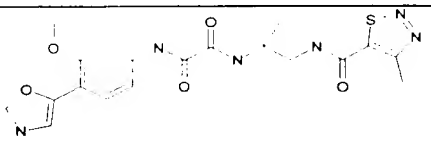
225.		443.0
226.		443.0
227.		443.1
228.		443.1
229.		451.0
230.		451.0
231.		457.1
232.		462.0
233.		482.0
234.		428.0
235.		429.1

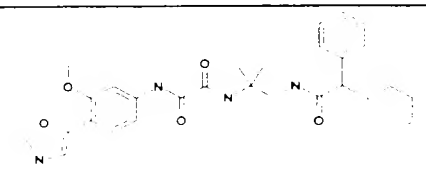
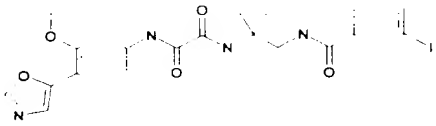
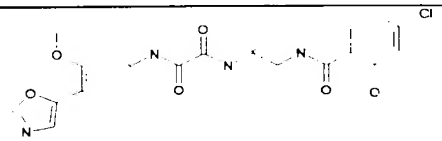
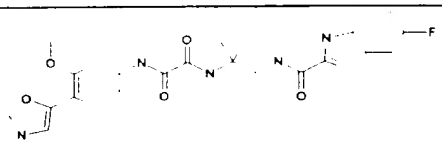
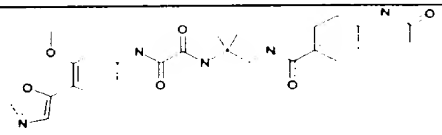
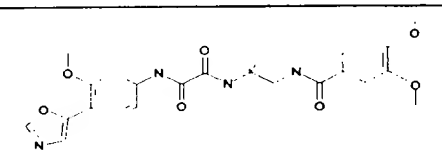
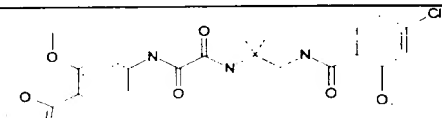
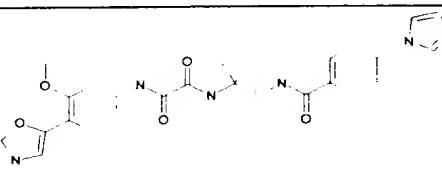
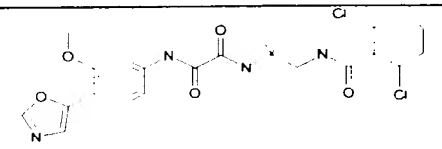
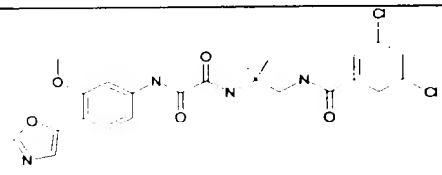
236.		431.0
237.		440.0
238.		445.0
239.		455.0
240.		455.0
241.		457.1
242.		467.1
243.		471.0
244.		471.0
245.		471.0
246.		482.0

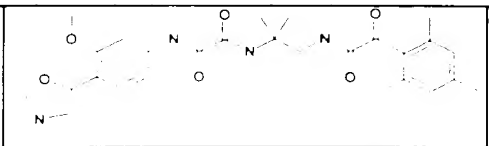
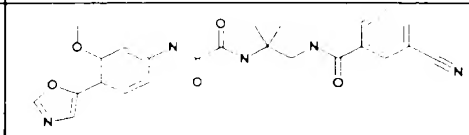
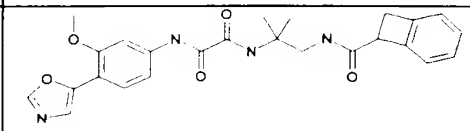
247.		487.1
248.		476.1
249.		477.1
250.		479.1
251.		479.1
252.		480.1
253.		480.1
254.		431.1
255.		443.0
256.		444.0
257.		444.0

258.		487.1
259.		505.1
260.		463.0
261.		467.1
262.		472.0
263.		473.0
264.		391.0
265.		401.0
266.		405.0
267.		431.1

268.		433.0
269.		441.0
270.		441.0
271.		441.0
272.		442.0
273.		442.0
274.		442.0
275.		453.0
276.		453.0
277.		453.0
278.		453.0

279.		453.0
280.		454.0
281.		455.0
282.		455.0
283.		455.0
284.		457.0
285.		457.0
286.		457.1
287.		457.1
288.		459.0

289.		527.2
290.		563.0
291.		487.0
292.		494.1
293.		494.1
294.		497.1
295.		501.0
296.		502.1
297.		505.0
298.		505.0

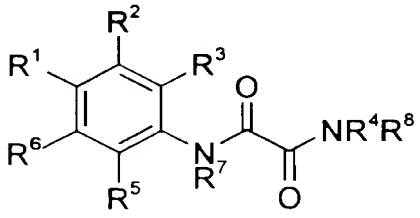
299.		507.1
300.		462.0
301.		463.1

In the present specification "comprise" means "includes or consists of" and "comprising" means "including or consisting of".

The features disclosed in the foregoing description, or the following claims, or the accompanying drawings, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for attaining the disclosed result, as appropriate, may, separately, or in any combination of such features, be utilised for realising the invention in diverse forms thereof.

CLAIMS:

1. Compounds of the general formula



(I)

wherein

R^1 represents heterocyclyl;

R^2 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, hydroxy or cyano;

R^3 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^4 represents hydrogen, lower alkyl, lower cycloalkyl, aryl, or heterocyclyl;

R^5 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^6 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^7 represents hydrogen, or unsubstituted lower alkyl;

R^8 represents hydrogen, or unsubstituted lower alkyl;

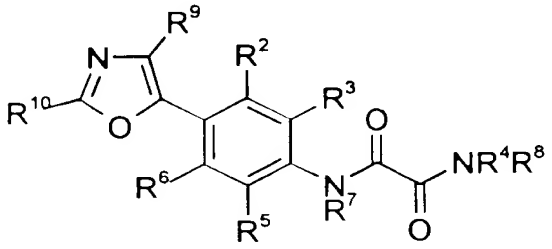
or R^4 and R^8 together with the nitrogen atom to which they are attached represent heterocyclyl;

and pharmaceutically acceptable salts thereof.

2. Compounds according to Claim 1 wherein at least one of R^2, R^3, R^5 and R^6 is not hydrogen.

3. Compounds according to Claim 1 or Claim 2 wherein R^1 represents an optionally substituted oxazole ring.

4. Compounds according to any one of the preceding claims wherein R^1 represents an optionally substituted oxazole ring, according to the general formula:



(IX)

wherein R^2 to R^8 are defined as in Claim 1, and

R^9 represents hydrogen, lower alkyl, or aryl-lower alkyl;

R^{10} represents hydrogen.

5. Compounds according to Claim 4 wherein R^9 represents methyl, ethyl or benzyl.

6. Compounds according to Claim 4 wherein R^9 and R^{10} are hydrogen.

7. Compounds according to Claim 1 or Claim 2 wherein R^1 represents triazolyl.

8. Compounds according to any one of the preceding claims wherein R^2 is lower alkoxy.

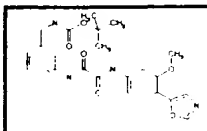
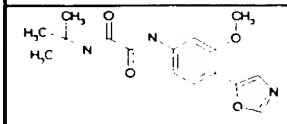
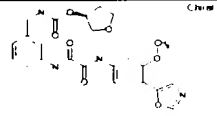
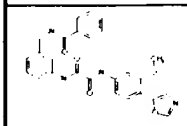
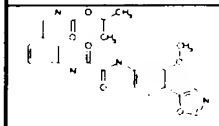
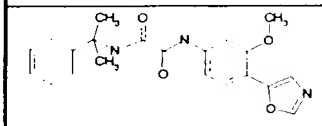
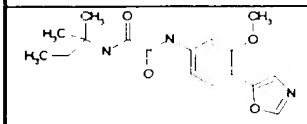
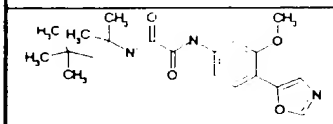
9. Compounds according to claim 8 wherein R^2 is methoxy.

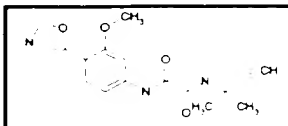
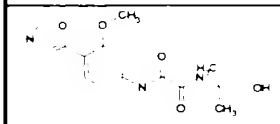
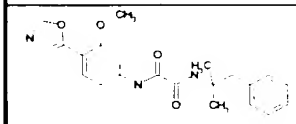
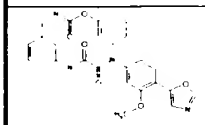
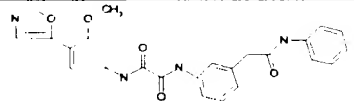
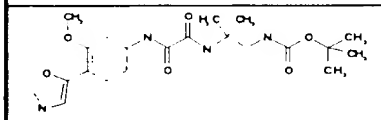
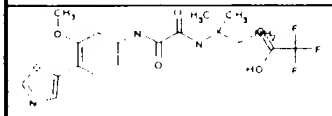
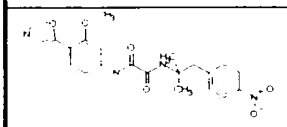
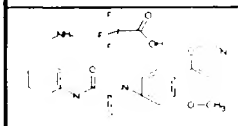
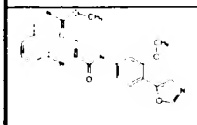
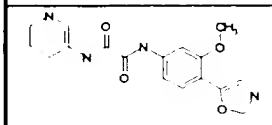
10. Compounds according to any one of the preceding claims wherein R^4 represents a lower alkyl group which is branched.

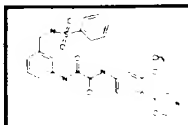
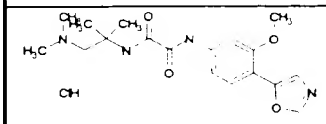
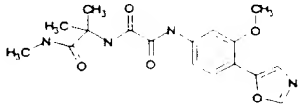
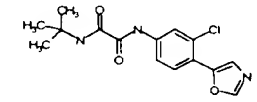
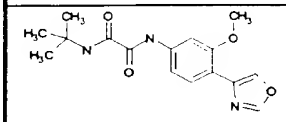
11. Compounds according to any one of the preceding claims wherein R^7 is hydrogen.

12. Compounds according to any one of the preceding claims wherein R^8 is hydrogen.

13. A compound according to any one of claims 1, 2, 3, 4, or 6, selected from:

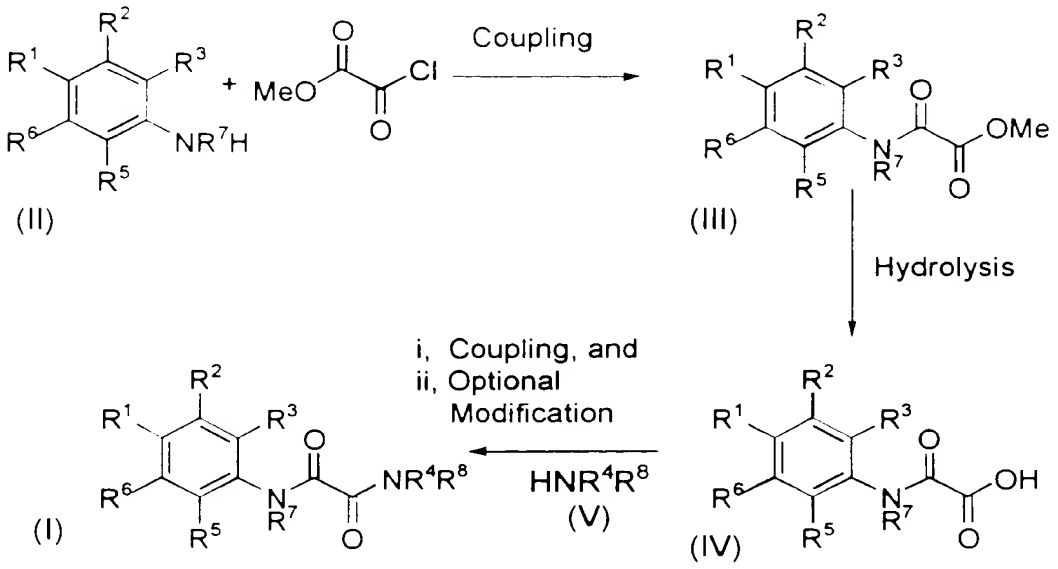
	tert-Butyl [3-[[[3-methoxy-4-(5-oxazolyl) anilino]oxalyl]amino]benzyl]carbamate
	N-tert-Butyl-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide
	[3-[[[3-Methoxy-4-(5-oxazolyl)anilino] oxalyl]amino]benzyl]carbamic acid tetrahydro-3(S)-furyl ester
	N-[3-(Benzamidomethyl)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide
	Isopropyl [3-[[[3-methoxy-4-(5-oxazolyl) anilino]oxalyl]amino]benzyl]carbamate
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-(1-methyl-1-phenylethyl)oxalamide
	N-(1,1-Dimethylpropyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-(1,1,3,3-tetramethyl-butyl)oxalamide

	N-(1,1-Dimethylpropargyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide
	N-(2-Hydroxy-1,1-dimethylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide
	N-(1,1-Dimethyl-2-phenylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide
	Phenyl [3-[[[4-(5-oxazolyl)anilino] oxalyl]amino]benzyl]carbamate
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[3-[(phenylcarbamoyl)methyl] phenyl]oxalamide
	tert-Butyl [2-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]-2-methylpropyl]carbamate
	N-(2-Amino-1,1-dimethylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate (1:1)
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[1,1-dimethyl-2-(4-nitrophenyl) ethyl]oxalamide
	N-[3-(Aminomethyl)phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide trifluoroacetate (1:1)
	Methyl [3-[[[3-methoxy-4-(5-oxazolyl)anilino]oxalyl]amino]benzyl]carb amate
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-(3-pyridyl)oxalamide

	N-[3-[(Benzenesulfonamido)methyl]phenyl]-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide
	N-(2-Dimethylamino-1,1-dimethylethyl)-N'-[3-methoxy-4-(5-oxazolyl)phenyl]oxalamide hydrochloride (1:1)
	N-[3-Methoxy-4-(5-oxazolyl)phenyl]-N'-[1-methyl-1-(methylcarbamoyl)ethyl]oxalamide
	N-tert-Butyl-N'-[3-chloro-4-(5-oxazolyl)phenyl]oxalamide
	N-tert-Butyl-N'-[3-methoxy-4-(4-oxazolyl)phenyl]oxalamide

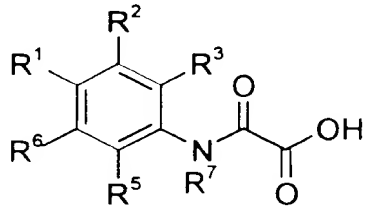
or a pharmaceutically acceptable salt thereof.

14. A process for the manufacture of the compounds of formula (I) claimed in any one of claims 1 to 13 and their pharmaceutically acceptable salts, which process comprises the general reaction scheme:



wherein R^1 to R^8 are defined as in Claim 1, and, optionally, converting the compound of formula (I) into a pharmaceutically acceptable salt.

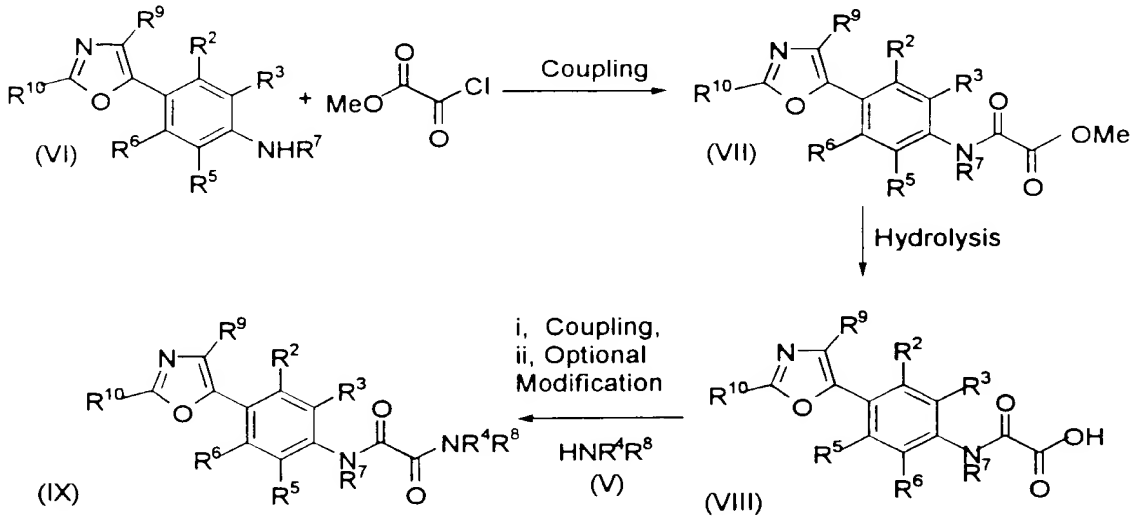
15. Compounds of the general formula



(IV)

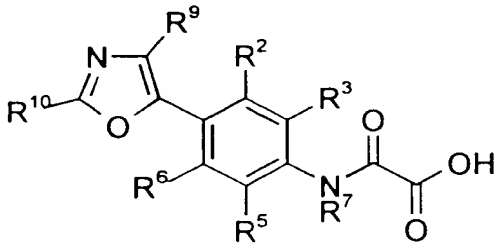
wherein R^1, R^2, R^3, R^5, R^6 and R^7 are defined as in Claim 1.

16. A process for the manufacture of the compounds claimed in Claim 4, and their pharmaceutically acceptable salts, which process comprises the general reaction scheme:



wherein R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are defined as in Claim 1, and R^9 and R^{10} are defined as in Claim 4, and, optionally, converting the compound of formula (IX) into a pharmaceutically acceptable salt.

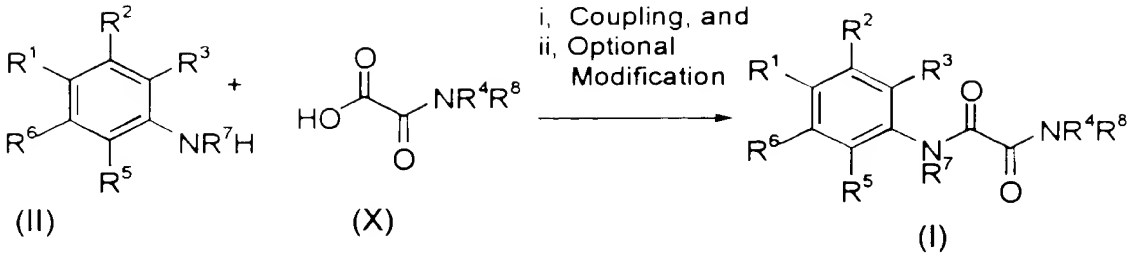
17. Compounds of the general formula



(VIII)

wherein R^2, R^3, R^5, R^6 and R^7 are defined as in Claim 1, and R^9 and R^{10} are defined as in Claim 4.

18. A process for the manufacture of the compounds of formula (I) claimed in any one of claims 1 to 13 and their pharmaceutically acceptable salts, which process comprises the general reaction scheme:



(II) (X) (I)

wherein R^1 to R^8 are defined as in Claim 1, and, optionally, converting the compound of formula (I) into a pharmaceutically acceptable salt.

19. Compounds according to any one of claims 1 to 13 and their pharmaceutically acceptable salts, when manufactured according to the process claimed in claim 14 or claim 18 or according to a process equivalent thereto.

20. Compounds according to Claim 4, and their pharmaceutically acceptable salts, when manufactured according to the process claimed in claim 16 or according to a process equivalent thereto.

21. A phamaceutical composition comprising a compound according to any one of Claims 1 to 13, 19 or 20, or its pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent or adjuvant, and, optionally, one or more additional therapeutically active substance(s).

22. A pharmaceutical composition according to Claim 21, wherein the one or more additional therapeutically active substance(s) is an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-parasitic agent, an anti-fungal agent, an anti-inflammatory agent and/or an anti-vascular hyperproliferation agent.

23. A pharmaceutical composition according to Claim 22, wherein the one or more additional therapeutically active substance(s) is interferon or a derivative thereof.

24. A compound according to any one of Claims 1 to 13, 19 or 20, or its pharmaceutically acceptable salt, or a composition according to any one of Claims 21 to 23, for use in therapy.

25. A compound according to Claim 24 for use in monotherapy.

26. A compound according to Claim 24 for use in combination therapy.

27. A process for the production of a medicament, which process comprises bringing a compound according to any one of Claims 1 to 13, 19 or 20, or a pharmaceutically acceptable salt thereof into a galenical administration form together with a pharmaceutically acceptable carrier, diluent or adjuvant and, optionally, one or more additional therapeutically active substance(s).

28. A process according to Claim 27, wherein the one or more additional therapeutically active substance(s) is an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-parasitic agent, an anti-fungal agent, an anti-inflammatory agent and/or an anti-vascular hyperproliferation agent.

29. A process according to Claim 28, wherein the one or more additional therapeutically active substance(s) is interferon or a derivative thereof.

30. A method of treating an immune mediated condition or disease, a viral disease, a bacterial disease, a parasitic disease, inflammation, an inflammatory disease, a hyperproliferative vascular disease, a tumour, or cancer in a subject, comprising the step of administering to the subject a therapeutically effective amount of a compound according to any one of Claims 1 to 13, 19 or 20, or its pharmaceutically acceptable salt, or a pharmaceutical composition according to any one of Claims 21 to 23.

31. A method of treating an immune mediated condition or disease, a viral disease, a bacterial disease, a parasitic disease, inflammation, an inflammatory disease, a

hyperproliferative vascular disease, a tumour, or cancer in a subject, comprising the steps of (a) administering to the subject a therapeutically effective amount of a compound according to any one of Claims 1 to 13, 19 or 20, or its pharmaceutically acceptable salt, and (b) concurrently or sequentially administering to the subject one or more additional therapeutically active substance(s).

32. A method according to Claim 31, wherein the one or more additional therapeutically active substance(s) is selected from the group consisting of an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-parasitic agent, an anti-fungal agent, an anti-inflammatory agent and an anti-vascular hyperproliferation agent.

33. A method according to Claim 32, wherein the one or more additional therapeutically active substance(s) is interferon or a derivative thereof.

34. The use of a compound according to any one of Claims 1 to 13, 19 or 20, or its pharmaceutically acceptable salt, alone, or concurrently or sequentially, with one or more additional therapeutically active substance(s), in a method of treatment, especially in the treatment of an immune mediated condition or disease, a viral disease, a bacterial disease, a parasitic disease, inflammation, an inflammatory disease, a hyperproliferative vascular disease, a tumour, or cancer.

35. The use of a compound according to any one of Claims 1 to 13, 19 or 20, for the manufacture of a medicament for use in a method of treatment, especially for use in treating an immune mediated condition or disease, a viral disease, a bacterial disease, a parasitic disease, inflammation, an inflammatory disease, a hyperproliferative vascular disease, a tumour, or cancer.

36. The use according to Claim 35, wherein the medicament is for concurrent or sequential administration with one or more additional therapeutically active substance(s).

37. The use of a compound according to any one of Claims 1 to 13, 19 or 20, in combination with one or more additional therapeutically active substance(s) for the manufacture of a medicament for use in a method of treatment, especially for use in treating an immune mediated condition or disease, a viral disease, a bacterial disease, a parasitic disease, inflammation, an inflammatory disease, a hyperproliferative vascular disease, a tumour, or cancer.

38. The use according to any one of Claims 34 to 37, for treating an immune mediated condition or disease, especially for treating an autoimmune disease, a graft versus host disease, or transplant rejection.

39. The use according to any one of Claims 34 to 37, for treating a viral disease, especially for treating a viral disease wherein the virus is orthomyxovirus, paramyxovirus, herpesvirus, retrovirus, flavirus, pestivirus, hepatrophic virus, bunyavirus, Hantaan virus, Caraparu virus, human papilloma virus, encephalitis virus, arena virus, reovirus, vesicular stomatitis virus, rhinovirus, enterovirus, Lassa fever virus, togavirus, poxvirus, adenovirus, rubiola virus, rubella virus, or hepatitis virus.

40. The use according to Claim 39, wherein the virus is hepatitis C.

41. The use according to Claim 39, wherein the virus is HIV.

42. The use according to any one of Claims 34 to 37, for treating a hyperproliferative vascular disease, especially for treating a hyperproliferative vascular disease wherein the hyperproliferative vascular disease is restenosis, stenosis or artherosclerosis.

43. The use of any one of Claims 34 to 37, for the treatment of inflammation or an inflammatory disease, especially for the treatment of an inflammatory disease wherein the inflammatory disease is osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, or adult respiratory distress syndrome.

44. The use according to any one of Claims 34 to 37, for the treatment of a tumour or cancer, especially for the treatment of cancer wherein the cancer is lymphoma or leukaemia.

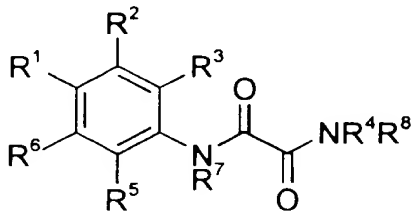
45. The use according to any one of Claims 34 or 36 to 44, wherein the one or more additional therapeutically active substance(s) is an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-parasitic agent, an anti-fungal agent, an anti-inflammatory agent and/or an anti-vascular hyperproliferation agent.

46. The use according to Claim 45, wherein the one or more additional therapeutically active substance(s) is interferon or a derivative thereof.

47. The invention hereinbefore described.

ABSTRACT

Disclosed are compounds of the general formula



(I)

wherein

R^1 represents heterocyclyl;

R^2 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, hydroxy or cyano;

R^3 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^4 represents hydrogen, lower alkyl, lower cycloalkyl, aryl, or heterocyclyl;

R^5 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^6 represents hydrogen, unsubstituted lower alkyl, lower alkoxy, halo, or cyano;

R^7 represents hydrogen, or unsubstituted lower alkyl;

R^8 represents hydrogen, or unsubstituted lower alkyl;

or R^4 and R^8 together with the nitrogen atom to which they are attached represent heterocyclyl; and pharmaceutically acceptable salts thereof. The disclosed oxamide derivatives are inhibitors of the enzyme inosine monophosphate dehydrogenase (IMPDH). They can be used as medicaments, especially for treating immune mediated conditions or diseases, viral diseases, bacterial diseases, parasitic diseases, inflammation, inflammatory diseases, hyperproliferative vascular diseases, tumours, and cancer. They can be used alone, or in combination with other therapeutically active agents, for example, an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-parasitic agent, an anti-inflammatory agent, an anti-fungal agent and/or an anti-vascular hyperproliferation agent.

SERIAL NO.
FILED:

[illegible]MANN-LA ROCHE INC.
[illegible]NGSLAND STREET
[illegible], NEW JERSEY 07110